

PROCESS OF PREPARING ESTERS AND ETHERS OF PROBUCOL AND DERIVATIVES THEREOF

This application claims priority to U.S. provisional Patent Application Serial No
5 60/439,665, filed January 13, 2003.

FIELD OF THE INVENTION

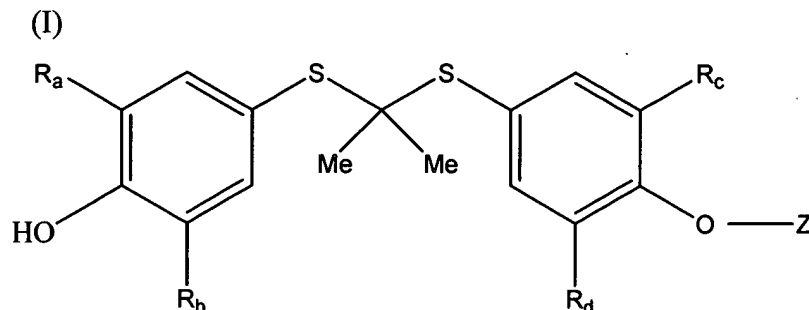
The present invention is a process for the manufacture of esters and ethers of
probucol and derivatives thereof that are suitable for the treatment of inflammatory and
10 cardiovascular diseases.

BACKGROUND OF THE INVENTION

U.S. Patent No. 5,262,439 to Parthasarathy, which is assigned to AtheroGenics,
15 Inc. discloses analogs of probucol with increased water solubility in which one or both of
the hydroxyl groups are replaced with ester groups that increase the water solubility of
the compound. The '439 patent reports that carboxylic acid derivatives of probucol can
be prepared by treating probucol with an excess of dicarboxylic acid anhydride and
catalytic amounts of 4-dimethyl-aminopyridine at a temperature sufficient to ensure that
20 the dicarboxylic acid anhydride is liquid. Under these conditions, no anhydrous solvent is
necessary, as the anhydride itself acts as a solvent.

WO 01/70757 filed by AtheroGenics, Inc. describes the use of certain compounds
of the following formula, and pharmaceutically acceptable salts thereof along with
method of use and methods of manufacturing:

25



wherein

- a) R_a , R_b , R_c , and R_d are independently any group that does not adversely affect the desired properties of the molecule, including hydrogen, alkyl, substituted alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, alkaryl, substituted alkaryl, aralkyl, or substituted aralkyl; and
- b) Z is (i) a substituted or unsubstituted carbohydrate, (ii) a substituted or unsubstituted alditol, (iii) C_{1-10} alkyl or substituted C_{1-10} alkyl, terminated by sulfonic acid, (iv) C_{1-10} alkyl or substituted C_{1-10} alkyl, terminated by phosphonic acid, (v) substituted or unsubstituted C_{1-10} alkyl-O-C(O)- C_{1-10} alkyl, (vi) straight chained polyhydroxylated C_{3-10} alkyl; (vii) $-(CR_2)_{1-6}-COOH$, wherein R is independently hydrogen, halo, amino, or hydroxy, and wherein at least one of the R substituents is not hydrogen; or (viii) $-(CR_2)_{1-6}-X$, wherein X is aryl, heteroaryl, or heterocycle, and R is independently hydrogen, halo, amino, or hydroxy.

US Patent No. 6,147,250, assigned to AtheroGenics, Inc., provides compounds, compositions, method for inhibiting the expression of VCAM-1, and methods of preparing said compounds and compositions. The patent reports that a monoester can be prepared by treating a quantity of probucol in a 0.1 M solution of tetrahydrofuran with 2 equivalents of sodium hydride and stirred at room temperature for 30 minutes. To the reaction mixture is added 3 equivalents of an acid chloride or acid anhydride and the reaction stirred at room temperature for 16 hours. The reaction is quenched with 1 N HCl and diluted with ethyl acetate. The aqueous layer is removed and the ethyl acetate layer is washed with water and then with an aqueous saturated sodium chloride solution. The ethyl acetate solution is dried over magnesium sulfate, gravity or vacuum filtered, and then concentrated. The product is purified by silica gel chromatography yielding 14% of the desired compound.

U.S. Patent No. 6,323,359 discloses and claims methods of manufacturing a group of compounds found in the '250 patent. The '359 patent discloses the use of alkali metal hydroxide, alkali metal alkoxide, alkali ammonium alkoxide, alkyl ammonium hydroxide

to form alkali metal salts of probucol compounds and then reacting the salts with dicarboxylic acid anhydride.

French Patent Publication No. 2.168.137 describes the production of diesters of probucol by reacting probucol with a halide or anhydride of an organic acid in an inert
5 solvent with heat and in the presence of a base such as an alkaline hydroxide or carbonate, a tertiary amine or a tertiary nitrogenous heterocycle. The O-metallic derivative of probucol can also be used as the reaction intermediate.

What is still needed is a method of manufacturing a group of compounds described in U.S. Patent Nos. 6,141,250; 6,323,359; 5,262,439; and WO 01/70757 that is
10 efficient and gives good yields.

It is another object of the invention to provide a process for the preparation of monoesters and monoethers of probucol or a probucol derivative that optimizes the amount of final product.

It is yet another object of the present invention to provide a process for the
15 preparation of monoesters and monoethers of probucol or a probucol derivative that minimizes the amount of reagent used.

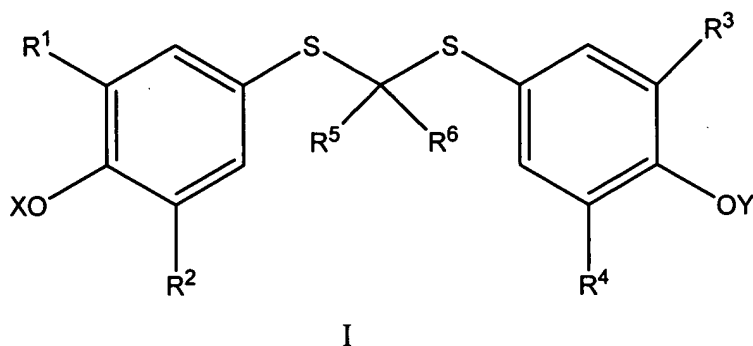
SUMMARY OF THE INVENTION

20 A process for the preparation of esters and ethers of probucol or a probucol derivative is provided that optimizes the amount of monoester in the final product mixture and minimizes the amount of reagents.

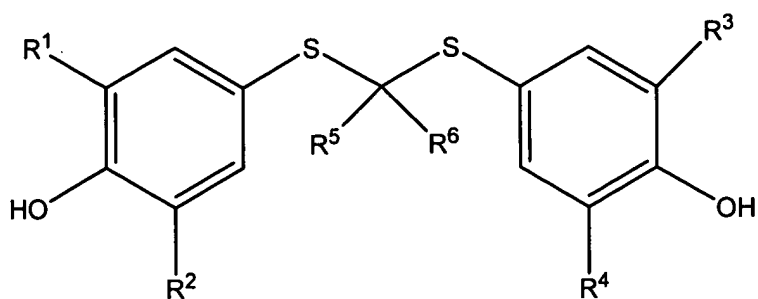
It has been discovered that probucol or a derivative thereof can be efficiently converted to esters of probucol by reacting a free hydroxyl-containing probucol or a
25 derivative thereof (by which is meant a probucol compound with at least one substituent that is different from that on the parent probucol molecule but which maintains the two free hydroxyl groups) with a Grignard reagent or a lithium reagent that produces a magnesium salt or lithium salt of probucol or the probucol derivative, respectively. The probucol compound salt with strong oxide anion is then reacted with an ester forming
30 compound such as a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride, a saturated or unsaturated activated carboxylic acid ester or

other ester-forming reagent. The probucol compound salt can alternatively be reacted with an ether forming compound to generate a probucol ether or probucol ether derivative.

In a broad description, the invention consists of processes to manufacturing a
 5 compound of Formula I and salts thereof



- 10 wherein R^1 , R^2 , R^3 , and R^4 are independently selected from the group consisting of hydrogen and alkyl, said alkyl optionally substituted by hydroxy, alkyl, alkenyl, acyl, nitro, amino, halo, carboxy and cyano;
 R^5 and R^6 are the same or different and independently selected from the group consisting of alkyl, alkenyl, and aryl all of which can be optionally substituted by hydroxy, alkyl,
 15 alkenyl, acyl, nitro, amino, halo, carboxy and cyano;
 R^5 and R^6 can come together to form a carbocyclic ring;
 X is selected from the group consisting of hydrogen, an optionally substituted unsaturated acyl, and an optionally substituted saturated acyl, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged
 20 functionality;
 Y is selected from the group consisting of an optionally substituted unsaturated acyl and an optionally substituted saturated acyl, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged
 functionality;
 25 comprising:
 reacting a compound of Formula II



II

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all
 5 which can be optionally substituted, to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of
 10 protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula I or salts thereof; or

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl, and an optionally substituted saturated alkyl, said optionally substituted unsaturated
 15 alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl, and an optionally substituted saturated alkyl, said optionally substituted unsaturated alkyl and
 20 optionally substituted saturated alkyl optionally containing a polar or charged functionality;

comprising:

reacting a compound of Formula II wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the
 25 group consisting of alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl

lithium, and a heteroaryl lithium, all which can be optionally substituted, to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-

5 sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy, epoxide and cyano;

10 separating and isolating said compound of Formula I or salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

A process for the preparation of an ester of probucol or a probucol derivative is provided that optimizes the amount of final product and minimizes the amount of

15 reagents used.

Probucol or a probucol derivative thereof can be converted to a monoester of probucol or probucol derivative by reacting the probucol or probucol derivative thereof with a Grignard reagent or a lithium reagent that produces a magnesium salt or lithium salt of probucol or the probucol derivative, respectively. The resulting probucol salt is
20 then reacted with an ester forming compound such as a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride, a saturated or unsaturated activated carboxylic acid ester or other ester-forming reagent, all of which may be optionally substituted.

Product ratios of about 64% monoester (wherein 66% monoester constitutes the expected theoretical yield), about 13% diester and about 23% unreacted probucol or
25 probucol derivative can be achieved by the optimized selection of reaction conditions.

In another embodiment, the invention provides a process for the preparation of an ester of probucol or a probucol derivative that optimizes the amount of the final product and minimizes the amount of reagents used.

Probucol or a probucol derivative can be converted to a monoether of probucol or probucol derivative by reacting the probucol or probucol derivative thereof with a Grignard reagent or a lithium reagent that produces a magnesium salt or lithium salt of probucol or the probucol derivative, respectively. The resulting probucol salt is then
5 reacted with an ether forming compound such as an alkyl halide, alkyl tosylate, alkyl mesylate, other alkyl group with an appropriate leaving group or other ether-forming reagent, all of which may be optionally substituted.

Any solvent can be used that achieves the desired results. Examples of solvents include any organic solvent that is inert under the reaction conditions, aprotic solvents,
10 ethers (such as THF or ethyl ether), liquid amides (such as DMF), hydrocarbons (including aromatic hydrocarbons such as toluene) and mixtures thereof. The word solvent as used herein includes mixtures of solvents. Solubilizing reagents as used herein include but are not limited to tetramethylurea; 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone and hexamethylphosphoramide. Generally, alcohols or other reagents that
15 could react with a Grignard reagent or lithium reagent should be avoided.

Typically the reaction is carried out in an inert atmosphere such as under a nitrogen or argon blanket.

In the first step of the reaction, probucol or a probucol derivative is mixed with a Grignard reagent or lithium reagent in the presence of a solvent, co-solvent or solubilizing
20 reagent or mixtures thereof to form a probucol salt.

In the second step, the probucol salt is reacted with the ester or ether forming agent. The probucol salt of the first step can be isolated and used in the second step at a later time or both the first and second steps can take place in a single reaction vessel by simply introducing the ester or ether forming reagent either neat or in a suitable solvent to
25 the probucol salt mixture. Alternatively, the probucol salt mixture can be added to a reaction vessel that contains the ester or ether forming agent either neat or in an appropriate solvent.

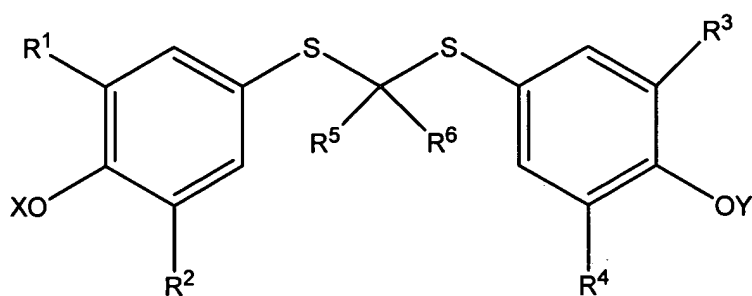
The first and second steps can be carried out at the same or different temperatures, or both or either can be reacted under gradient temperatures. Both steps generally are
30 carried out at any temperature(s) that achieve the desired results.

The reactions are maintained at low temperature, including any temperature to about or just above the freezing point of the solvent. In other embodiments, the temperature of either or both of the reactions range from below 0 °C to room temperature or higher, including up to the boiling point of the solvent. The selection of temperature
5 can depend on the preference of the operator, the available equipment, the freezing and boiling points of the solvent or solvents used, the reactivity of the reagents, and the control of side reactions.

Alternatively, the natural exotherm of either or both of the reactions are used to warm the reaction and to avoid the need for external application of heat. Excessive or
10 undesired exotherms may be controlled with external cooling.

In another aspect of the invention, a Grignard reagent or a lithium reagent is added to a mixture containing probucol or a probucol derivative and an ester or ether forming agent in a solvent, co-solvent, or solubilizing agent or mixtures thereof.

In a particularly broad form, the invention encompasses methods of
15 manufacturing compounds of Formula I or salts thereof



I

20 wherein R¹, R², R³, and R⁴ are independently selected from the group consisting of hydrogen and alkyl, said alkyl optionally substituted by hydroxy, alkyl, alkenyl, acyl, nitro, amino, halo, carboxy and cyano;

R⁵ and R⁶ are the same or different and independently selected from the group consisting of alkyl, alkenyl, and aryl all of which can be optionally substituted by hydroxy, alkyl,
25 alkenyl, acyl, nitro, amino, halo, carboxy and cyano;

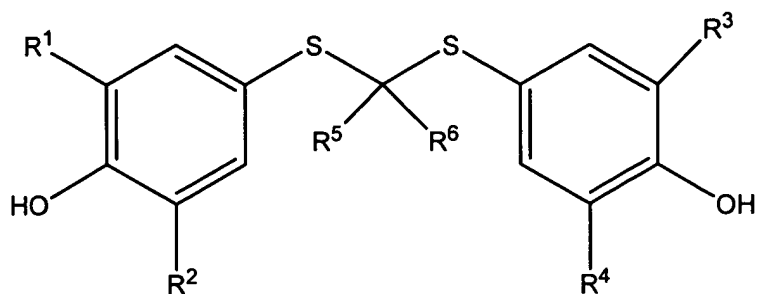
R⁵ and R⁶ can come together to form a carbocyclic ring;

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated acyl, and an optionally substituted saturated acyl, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

- 5 Y is selected from the group consisting of an optionally substituted unsaturated acyl and an optionally substituted saturated acyl, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

comprising:

- 10 reacting a compound of Formula II



II

wherein R¹, R², R³, R⁴, R⁵ and R⁶ are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all

15 which can be optionally substituted, to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of

- 20 protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula I or salts thereof; or

- X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl, and an optionally substituted saturated alkyl, said optionally substituted unsaturated
- 25

alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl, and an optionally substituted saturated alkyl, said optionally substituted unsaturated alkyl and
5 optionally substituted saturated alkyl optionally containing a polar or charged functionality;

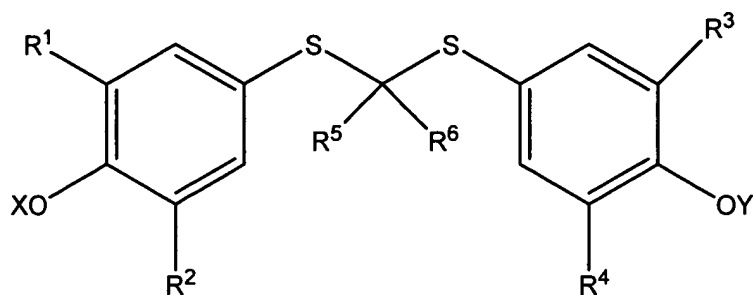
comprising:

reacting a compound of Formula II wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the
10 group consisting of alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted, to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated
15 alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy, epoxide and cyano;

20 separating and isolating said compound of Formula I or salts thereof.

In a 1st narrowed embodiment, the invention encompasses processes of manufacturing compounds of Formula I or salts thereof



I

wherein R^1 , R^2 , R^3 , and R^4 are the same or different and independently selected from the group consisting of hydrogen and an alkyl having from 1 to 6 carbon atoms;

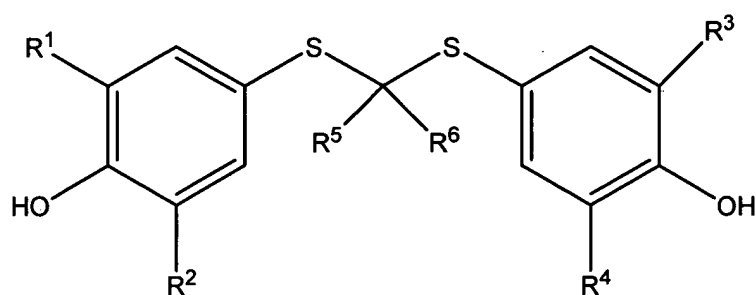
R^5 and R^6 are the same or different and independently selected from the group consisting of an alkyl having from 1 to 8 carbon atoms, an alkenyl having from 2 to 8 carbon atoms, and aryl;

R^5 and R^6 can come together to form a carbocyclic ring containing from 3 to 8 carbon atoms;

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms, and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula II



II

wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic

acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy and cyano;

5 separating and isolating said compound of Formula I or salts thereof; or

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and
10 optionally substituted saturated alkyl optionally containing a polar or charged functionality;

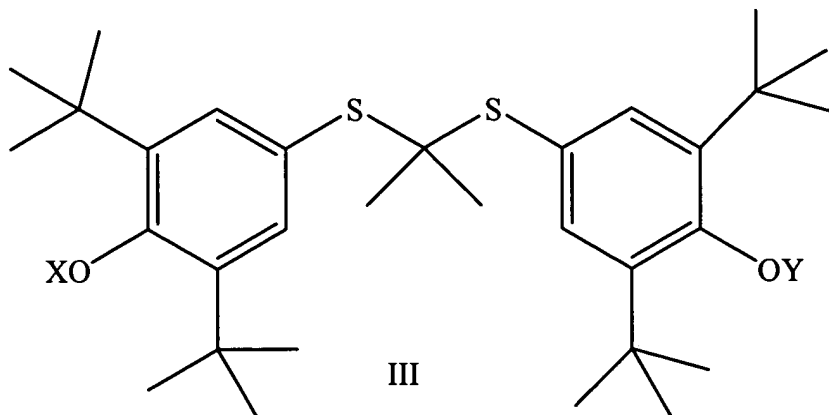
Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally
15 substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula II wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl
20 lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated
25 alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula I or salts thereof.

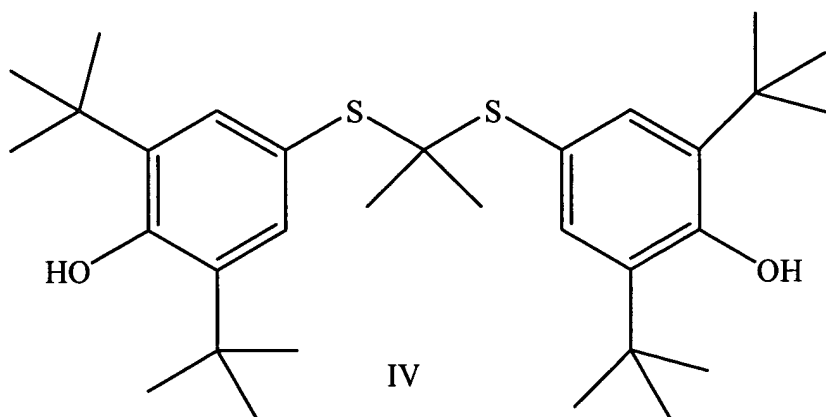
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In a 2nd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof



wherein:

- 5 X is selected from the group consisting of hydrogen, an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms, and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
- 10 Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:
- 15 reacting a compound of Formula IV



with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl

lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

10

In a 3rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

30

In a 4th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms, and an optionally substituted saturated acyl

5 having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having
10 from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of a

15 saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

20

In a 5th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl

25 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;

30 reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated acyl halide, saturated or unsaturated carboxylic acid anhydride

and a saturated or unsaturated activated carboxylic acid ester, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

5

In a 6th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
10 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
15 consisting of alkylmagnesium halide, alkenylmagnesium halide, alkynylmagnesium halide, arylmagnesium halide, arylalkylmagnesium halide, alkylmagnesium alkyl, arylmagnesium aryl, arylalkynylmagnesium halide, arylalkenylmagnesium halide, and heteroarylmagnesium halide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl,
20 nitro, protected amino, halo and protected carboxy, to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated carboxylic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
25 separating and isolating said compound of Formula III or salts thereof.

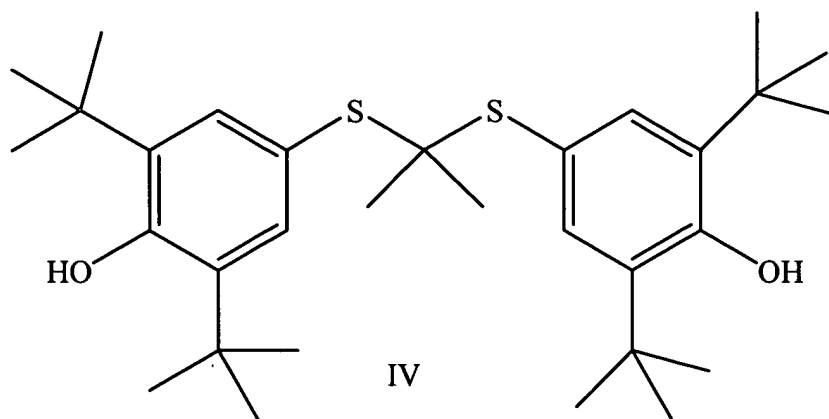
In a 7th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

30 Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having

from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
comprising:

reacting a solution of a compound of Formula IV



with a Grignard Reagent selected from the group consisting of alkylmagnesium halide, alkenylmagnesium halide, alkynylmagnesium halide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy, to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

In an 8th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having

from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from

- 5 the group consisting of Methylmagnesium bromide; Octadecylmagnesium chloride; Tetradecylmagnesium chloride; n-Pentadecylmagnesium bromide; Ethynylmagnesium chloride; n-Nonylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentyl magnesium chloride; Cyclopropylmagnesium bromide; (1-Methyl-2-propenyl)magnesium chloride; 1-Decylmagnesium bromide; 1-Octylmagnesium bromide; 1-Propynylmagnesium bromide; Dodecylmagnesium bromide; sec-Butylmagnesium chloride; 1-Propenylmagnesium bromide; Isopropenylmagnesium bromide; (2,2-Dimethylpropyl)magnesium chloride; 1-Heptylmagnesium bromide; 3-Butenylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium chloride; (2-Methyl-2-propenyl)magnesium chloride; Ethynylmagnesium bromide; 1-Hexylmagnesium bromide; Vinylmagnesium chloride; Allylmagnesium chloride; Ethylmagnesium chloride; n-Propylmagnesium chloride; Vinylmagnesium bromide; Allylmagnesium bromide; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide; 1-Propylmagnesium bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;
- 20 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
- 30 separating and isolating said compound of Formula III or salts thereof.

In a 9th embodiment, the invention is represented by the process of the 8th embodiment wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
5 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

10 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of Methylmagnesium bromide; Octadecylmagnesium chloride; Tetradecylmagnesium chloride; n-Nonylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentyl magnesium chloride; Cyclopropylmagnesium bromide; 1-Decylmagnesium bromide; 1-Octylmagnesium bromide; Dodecylmagnesium bromide; sec-
15 Butylmagnesium chloride; (2,2-Dimethylpropyl)magnesium chloride; 1-Heptylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium chloride; 1-Hexylmagnesium bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide; 1-Propylmagnesium
20 bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of
25 succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
30 separating and isolating said compound of Formula III or salts thereof.

In a 10th embodiment, the invention is represented by the process of the 9th embodiment

wherein:

X is hydrogen;

- 5 Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:
- 10 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of Methylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentylmagnesium chloride; Cyclopropylmagnesium bromide; 1-Octylmagnesium bromide; sec-Butylmagnesium chloride; (2,2-Dimethylpropyl)magnesium chloride; 1-
- 15 Heptylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium chloride; 1-Hexylmagnesium bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide; 1-Propylmagnesium bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and
- 20 Methylmagnesium chloride to form a magnesium salt;
- reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid
- 25 anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
- separating and isolating said compound of Formula III or salts thereof.

30

In an 11th embodiment, the invention is represented by the process of the 10th embodiment wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
5 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

10 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride;

Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Methylmagnesium iodide; n-Butylmagnesium chloride; tert-Butylmagnesium chloride; and

15 Methylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be
20 substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

25 In a 12th embodiment, the invention is represented by the process of the 11th embodiment wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally
30 substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a solution of a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

10

In a 13th embodiment, the invention is represented by the process of the 12th embodiment wherein:

X is hydrogen;

Y is a saturated acyl having from 1 to 10 carbon atoms or an optionally substituted

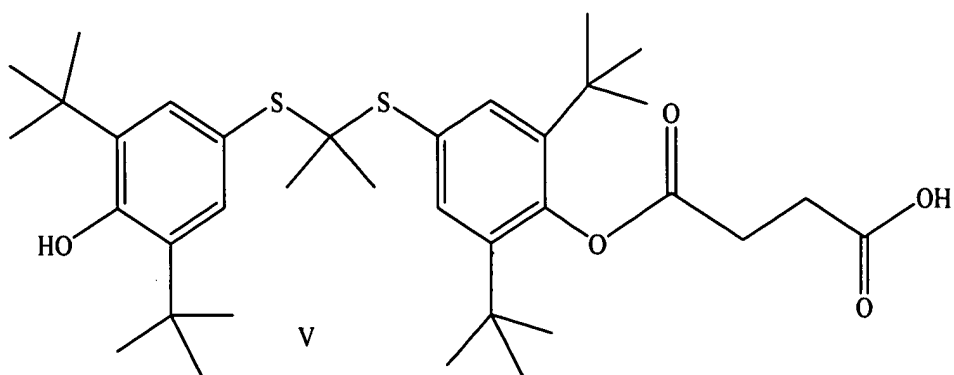
15 saturated acyl having from 1 to 10 carbon atoms, said saturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a solution of a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

20 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

25 separating and isolating said compound of Formula III or salts thereof.

In a 14th embodiment, the invention is represented by the process of the 13th embodiment to manufacture a compound of Formula V or salts thereof

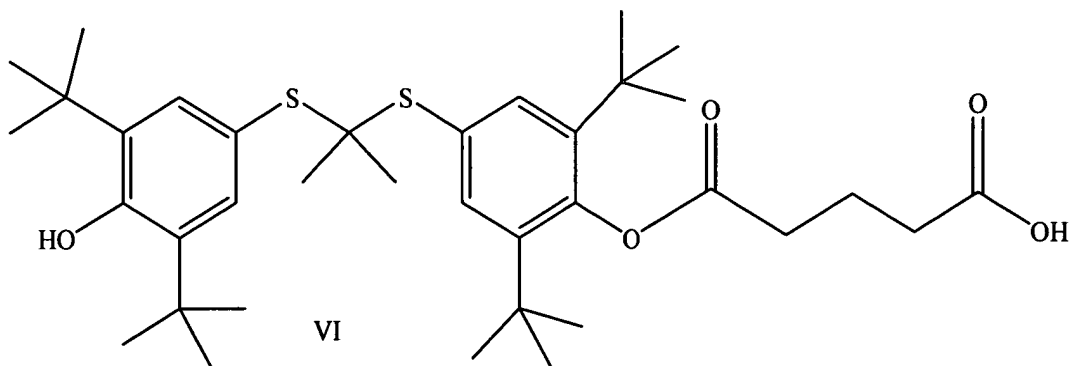


comprising:

reacting a solution of a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

- 5 reacting said magnesium salt with succinic acid anhydride;
- separating and isolating said compound of Formula V or salts thereof.

In a 15th embodiment, the invention is represented by the process of the 13th embodiment to manufacture a compound of Formula VI or salts thereof



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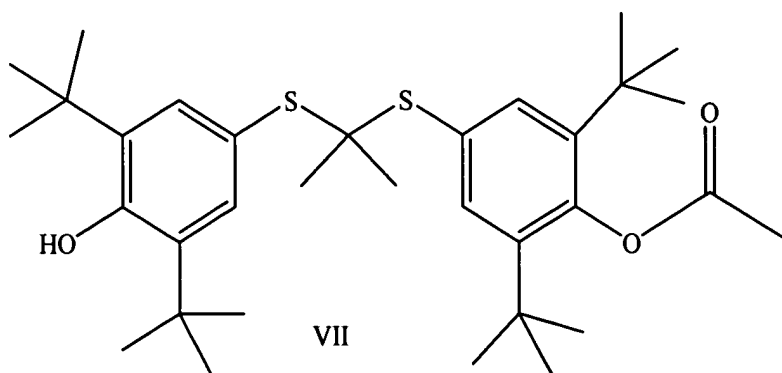
comprising:

reacting a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with glutaric acid anhydride;

- 15 separating and isolating said compound of Formula VI or salts thereof.

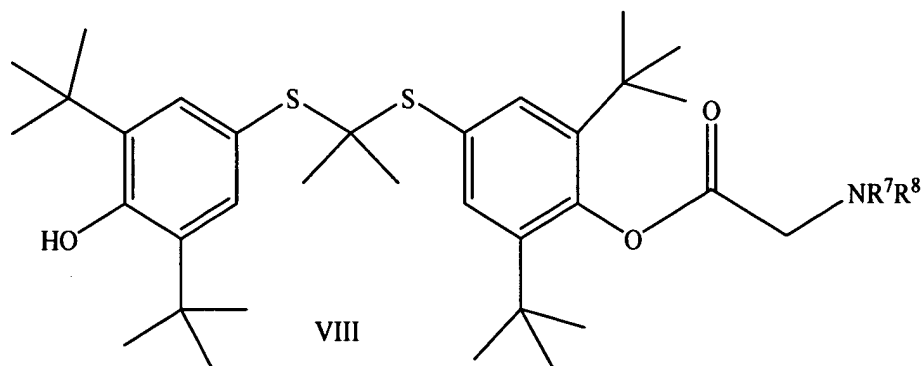
In a 16th embodiment, the invention is represented by the process of the 13th embodiment to manufacture a compound of Formula VII or salts thereof



comprising:

- reacting a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;
- 5 reacting said magnesium salt with acetic acid anhydride;
- separating and isolating said compound of Formula VII or salts thereof.

In a 17th embodiment, the invention is represented by the process of the 13th embodiment to manufacture a compound of Formula VIII or salts thereof



wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, aryl, aralkyl, Si(alkyl)₃, protected carboxy, alkylsulfonyl, and arylsulfonyl

comprising:

- 15 reacting a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;
- reacting said magnesium salt with acetic acid anhydride substituted by a protected or unprotected amino;
- separating and isolating said compound of Formula VIII or salts thereof

In an 18th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

- 5 Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:
- 10 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from arylmagnesium halide or heteroarylmagnesium halide to form a magnesium salt, wherein said arylmagnesium halide and heteroarylmagnesium halide may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;
- 15 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy,
- 20 alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

In a 19th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

25 X is hydrogen;

- Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
- 30 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
 consisting of 3-Chloro-4-fluorophenylmagnesium bromide; 3-Fluoro-2-
 methylphenylmagnesium bromide; 5-Fluoro-2-methoxyphenylmagnesium bromide; 5-
 Fluoro-2-methylphenylmagnesium bromide; 3,5-Dimethyl-4-methoxyphenylmagnesium
 5 bromide; 3-Fluoro-4-methylphenylmagnesium bromide; 3-
 [Bis(trimethylsilyl)amino]phenylmagnesium chloride; 3-Thienylmagnesium iodide; 3-
 Fluoro-4-chlorophenylmagnesium bromide; 3,4,5-Trifluorophenylmagnesium bromide;
 4-Methoxy-2-methylphenylmagnesium bromide; 2,4-Dimethoxyphenylmagnesium
 bromide; 2,3-Dimethylphenylmagnesium bromide; 3-Methylphenylmagnesium chloride;
 10 (4-methyl-1-naphthalenyl)magnesium bromide; (3-fluoro-4-methoxyphenyl)magnesium
 bromide; 2-Chloro-5-thienylmagnesium bromide; 3,4-Dimethylphenylmagnesium
 chloride; 3-Methyl-2-thienylmagnesium bromide; Pentamethylphenylmagnesium
 bromide; 3,4-Dimethoxyphenylmagnesium bromide; (3,4-Dimethylphenyl)magnesium
 bromide; (3,5-Dichlorophenyl)magnesium bromide; (4-Fluoro-3-
 15 methylphenyl)magnesium bromide; 3,4-Dichlorophenylmagnesium bromide; 2,3,5,6-
 Tetramethylphenylmagnesium bromide; 9-Phenanthryl magnesium bromide; (4-tert-
 Butylphenyl)magnesium bromide; 2,5-Dimethoxyphenylmagnesium bromide; 3,5-
 Difluorophenylmagnesium bromide; 4-Chlorophenylmagnesium chloride; (6-Methoxy-2-
 naphthyl)magnesium bromide; (2-Methoxy-1-naphthyl)magnesium bromide; 3-
 20 Methoxyphenylmagnesium bromide; (3-Chlorophenyl)magnesium bromide; (3,5-
 Dimethylphenyl)magnesium bromide; (2-Methylphenyl)magnesium chloride; 4-Fluoro-2-
 methylphenylmagnesium bromide; (2,5-Dimethylphenyl)magnesium bromide; m-
 Methylphenylmagnesium bromide; 4-Ethylphenylmagnesium bromide; 2-
 Pyridylmagnesium bromide; 4-Phenoxyphenylmagnesium bromide; 2-
 25 Naphthylmagnesium bromide; (2-Methyl-1-naphthyl)magnesium bromide; 2,6-
 Dimethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; 4-
 (Methylthio)phenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; 3,4-
 Methylenedioxyphenylmagnesium bromide; 3-Fluorophenylmagnesium bromide; (o-
 Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-
 30 Methoxyphenyl)magnesium bromide; 4-(Dimethylamino)phenylmagnesium bromide; 2-
 Thienylmagnesium bromide; (4-Methylphenyl)magnesium bromide; Mesitylmagnesium

bromide; 2-Tolylmagnesium bromide; Pentafluorophenylmagnesium bromide; (4-Chlorophenyl)magnesium bromide; 1-Naphthalenylmagnesium bromide; 4-Methylphenylmagnesium chloride; 4-Fluorophenylmagnesium bromide; Phenylmagnesium chloride; Phenylmagnesium bromide; and (4-Biphenyl)magnesium bromide to form a magnesium salt;
5 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy,
10 alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano; separating and isolating said compound of Formula III or salts thereof.

In a 20th embodiment, the invention is represented by the process to manufacture
15 a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
20 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3,5-Dimethyl-4-methoxyphenylmagnesium bromide; 4-Methoxy-2-methylphenylmagnesium bromide; 2,4-Dimethoxyphenylmagnesium bromide; 2,3-Dimethylphenylmagnesium bromide; 3-Methylphenylmagnesium chloride; 3,4-Dimethylphenylmagnesium chloride; Pentamethylphenylmagnesium bromide; 3,4-Dimethoxyphenylmagnesium bromide; (3,4-Dimethylphenyl)magnesium bromide; 2,3,5,6-Tetramethylphenylmagnesium bromide; (4-tert-Butylphenyl)magnesium bromide; 2,5-Dimethoxyphenylmagnesium bromide; 3-Methoxyphenylmagnesium bromide; (3,5-Dimethylphenyl)magnesium bromide; (2-Methylphenyl)magnesium chloride; (2,5-Dimethylphenyl)magnesium bromide; m-Methylphenylmagnesium bromide; 4-

- Ethylphenylmagnesium bromide; 4-Phenoxyphenylmagnesium bromide; 2,6-Dimethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; 3,4-Methylenedioxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; Mesitylmagnesium bromide; 2-Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium chloride; and Phenylmagnesium bromide to form a magnesium salt;
- reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
- separating and isolating said compound of Formula III or salts thereof.

In a 21st embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

- Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:
- reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methylphenylmagnesium chloride; (4-tert-Butylphenyl)magnesium bromide; 3-Methoxyphenylmagnesium bromide; (2-Methylphenyl)magnesium chloride; m-Methylphenylmagnesium bromide; 4-Ethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; 2-

Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium chloride; and Phenylmagnesium bromide to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid
5 anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
separating and isolating said compound of Formula III or salts thereof.

10

In a 22nd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
15 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
20 consisting of 3-Methylphenylmagnesium chloride; 3-Methoxyphenylmagnesium bromide; (2-Methylphenyl)magnesium chloride; m-Methylphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; 2-Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium
25 chloride; and Phenylmagnesium bromide to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be
30 substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

In a 23rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

5 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

10 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;

15 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

20 separating and isolating said compound of Formula III or salts thereof.

In a 24th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

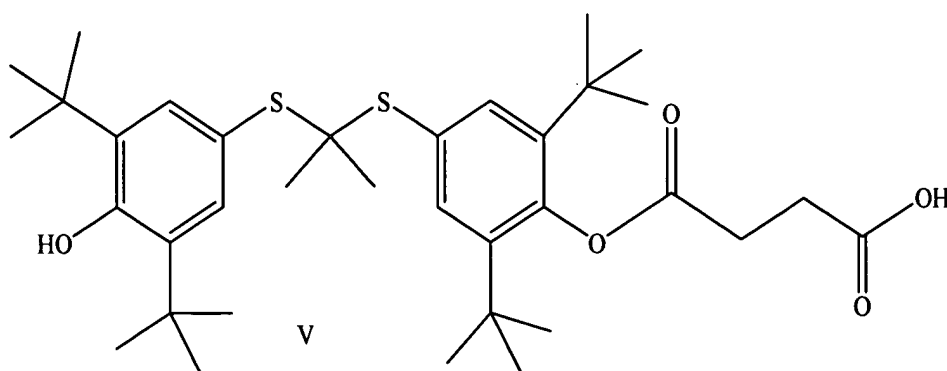
25 Y is a saturated acyl having from 1 to 10 carbon atoms or an optionally substituted saturated acyl having from 1 to 10 carbon atoms, said saturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

30 reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

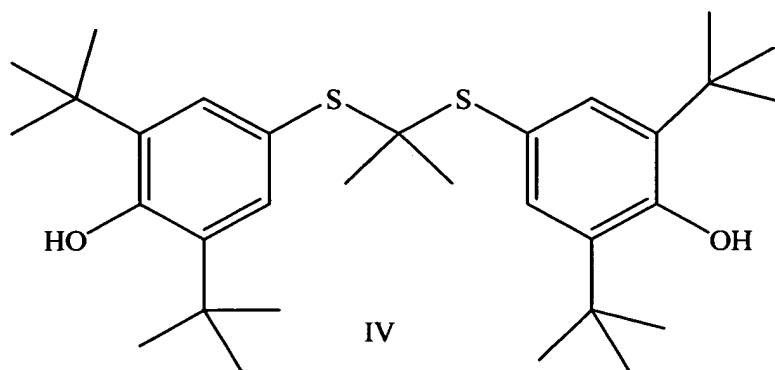
5 separating and isolating said compound of Formula III or salts thereof.

In a 25th embodiment, the invention is represented by the process to manufacture a compound of Formula V or salts thereof



comprising:

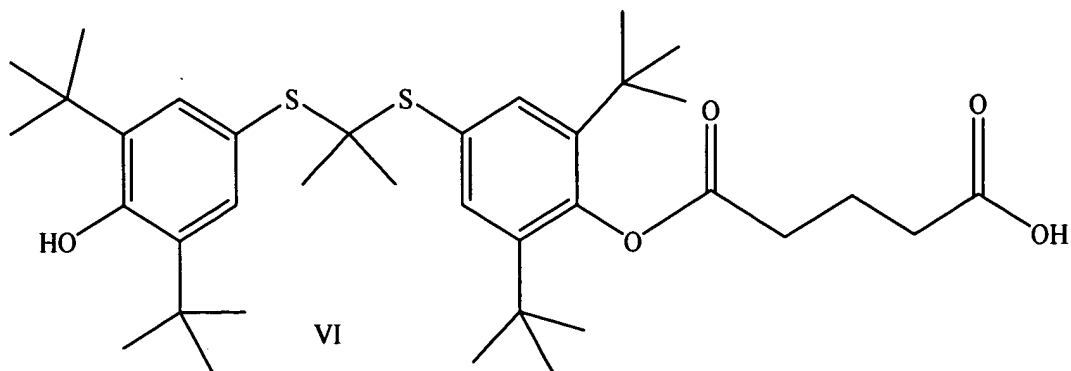
reacting a solution of a compound of Formula IV



with a Grignard Reagent selected from the group consisting of 3-

- 15 Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
- reacting said magnesium salt with succinic acid anhydride;
- separating and isolating said compound of Formula V or salts thereof.

In a 26th embodiment, the invention is represented by the process to manufacture a compound of Formula VI or salts thereof

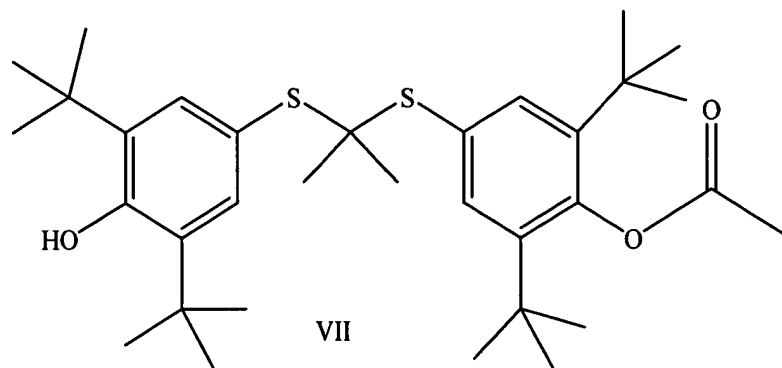


comprising:

- 5 reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
 reacting said magnesium salt with glutaric acid anhydride;
 separating and isolating said compound of Formula VI or salts thereof.

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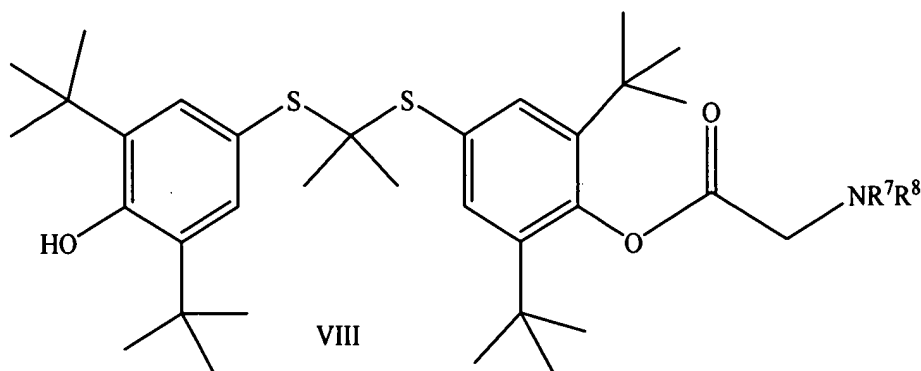
In a 27th embodiment, the invention is represented by the process to manufacture a compound of Formula VII or salts thereof



comprising:

- 15 reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
 reacting said magnesium salt with acetic acid anhydride;
 separating and isolating said compound of Formula VII or salts thereof.

In a 28th embodiment, the invention is represented by the process to manufacture a compound of Formula VIII or salts thereof



5 wherein R^7 and R^8 are independently selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, aryl, aralkyl, $\text{Si}(\text{alkyl})_3$, protected carboxy, alkylsulfonyl, and arylsulfonyl;

comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group

10 consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with acetic acid anhydride substituted by a protected or unprotected amino;

separating and isolating said compound of Formula VIII or salts thereof

15

In a 29th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof

wherein:

20 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

25 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of arylalkylmagnesium halide, arylalkynylmagnesium halide, and arylalkenylmagnesium halide to form a magnesium salt, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy,
5 alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;
reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be
10 substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
separating and isolating said compound of Formula III or salts thereof.

In a 30th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

15 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

20 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 2,5-Dimethylbenzylmagnesium chloride; 2,6-Dichlorobenzylmagnesium chloride; 2,4-Dichlorobenzylmagnesium chloride; 2-Fluorobenzylmagnesium chloride; 2,4-Dimethylbenzylmagnesium chloride; 3-Bromobenzylmagnesium bromide; 4-

25 Bromobenzylmagnesium bromide; (2-Phenylethyl)magnesium chloride; 3-Fluorobenzylmagnesium chloride; (3,4-Dichlorobenzyl)magnesium chloride; 2-Bromobenzylmagnesium bromide; 4-Methoxybenzylmagnesium chloride; 4-Methylbenzylmagnesium chloride; m-Methylbenzylmagnesium chloride; 2-Methylbenzylmagnesium chloride; 3-Chlorobenzylmagnesium chloride; 2-
30 Chlorobenzylmagnesium chloride; m-Methoxybenzylmagnesium chloride; Benzylmagnesium chloride; (Phenylethynyl)magnesium bromide; 4-

Fluorobenzylmagnesium chloride; Benzylmagnesium bromide; 4-Chlorobenzylmagnesium chloride; and 2-Chloro-6-fluorobenzylmagnesium chloride to form a magnesium salt;

- 5 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
- 10 separating and isolating said compound of Formula III or salts thereof.

In a 31st embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

- 15 Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:
- 20 reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 2,5-Dimethylbenzylmagnesium chloride; 2,4-Dimethylbenzylmagnesium chloride; (2-Phenylethyl)magnesium chloride; 4-Methoxybenzylmagnesium chloride; 4-Methylbenzylmagnesium chloride; m-Methylbenzylmagnesium chloride; 2-Methylbenzylmagnesium chloride; m-Methoxybenzylmagnesium chloride;
- 25 Benzylmagnesium chloride; and Benzylmagnesium bromide to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be
- 30 substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

In a 32nd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

5 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

10 comprising:

reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

15 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

20

In a 33rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

25 Y is a saturated acyl having from 1 to 10 carbon atoms or an optionally substituted saturated acyl having from 1 to 10 carbon atoms, said saturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;

comprising:

reacting a solution of a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

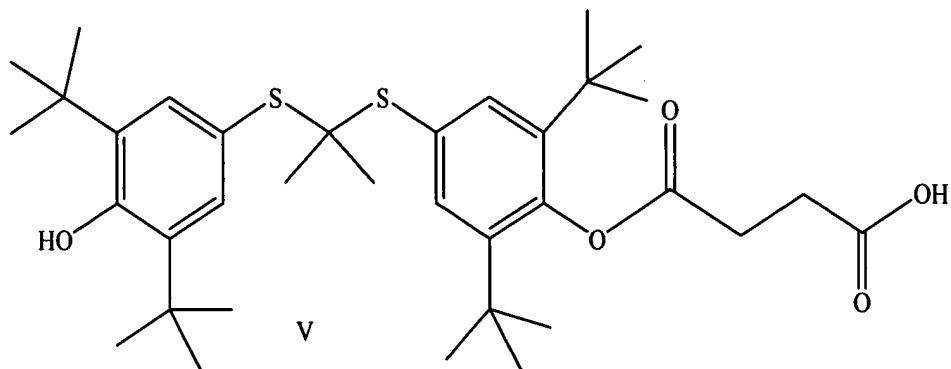
30 reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride and acetic acid anhydride, all of which

may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

separating and isolating said compound of Formula III or salts thereof.

5

In a 34th embodiment, the invention is represented by the process to manufacture a compound of Formula V or salts thereof



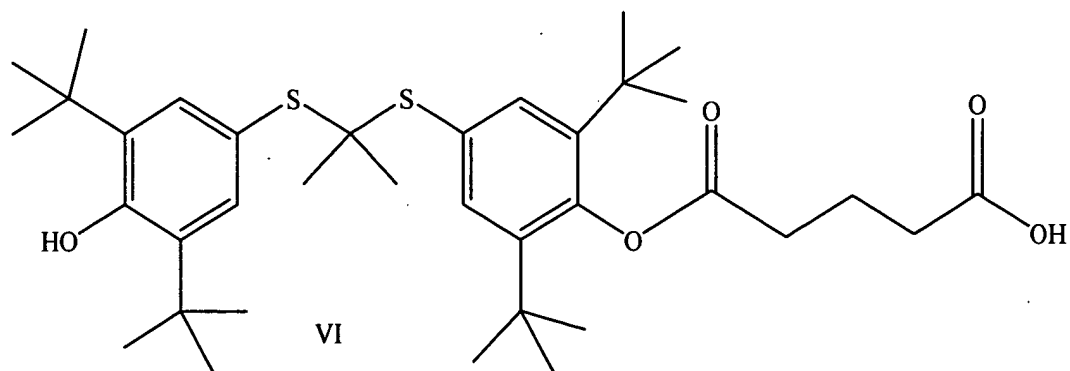
comprising:

10 reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with succinic acid anhydride;

separating and isolating said compound of Formula V or salts thereof.

15 In a 35th embodiment, the invention is represented by the process to manufacture a compound of Formula VI or salts thereof

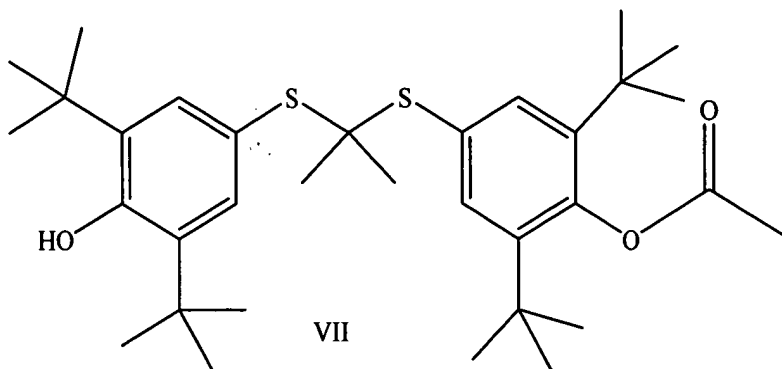


comprising:

reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with glutaric acid anhydride;
separating and isolating said compound of Formula VI or salts thereof.

5

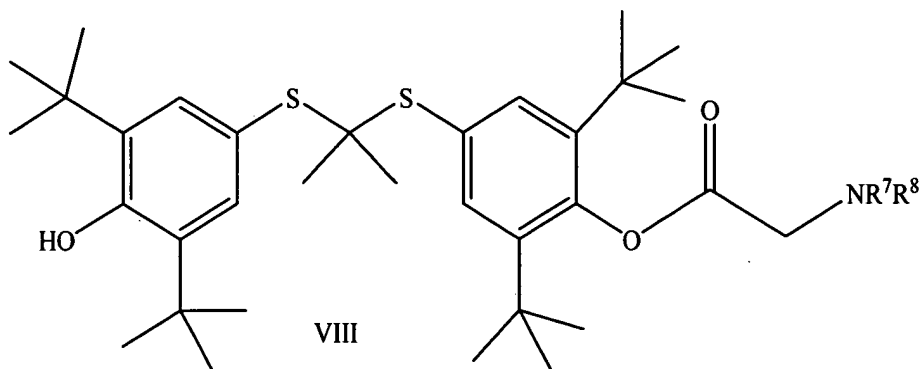
In a 36th embodiment, the invention is represented by the process to manufacture a compound of Formula VII or salts thereof



comprising:

- 10 reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with acetic acid anhydride;
separating and isolating said compound of Formula VII or salts thereof.

- 15 In a 37th embodiment, the invention is represented by the process to manufacture a compound of Formula VIII or salts thereof



wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen, acyl, alkyl, alkenyl, aryl, aralkyl, Si(alkyl)₃, protected carboxy, alkylsulfonyl, and arylsulfonyl

comprising:

- 5 reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with acetic acid anhydride substituted by a protected or unprotected amino;
separating and isolating said compound of Formula VIII or salts thereof

10

In a 38th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl

- 15 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from

- 20 alkylmagnesium alkyl or arylmagnesium aryl to form a magnesium salt, wherein said alkylmagnesium alkyl and arylmagnesium aryl may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;

reacting said magnesium salt with a compound selected from the group consisting of

- 25 succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride, maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

- 30 separating and isolating said compound of Formula III or salts thereof.

In a 39th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated acyl
5 having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

10 reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium; Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride, adipic acid anhydride, suberic acid anhydride, sebacic acid anhydride, azelaic acid anhydride, phthalic acid anhydride,
15 maleic acid anhydride, and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;
separating and isolating said compound of Formula III or salts thereof.

20 In a 40th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

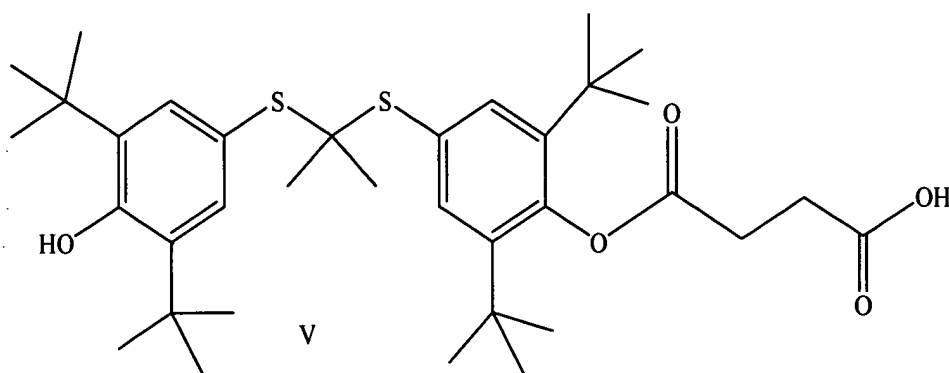
Y is selected from the group consisting of an optionally substituted unsaturated acyl
having from 1 to 18 carbon atoms and an optionally substituted saturated acyl having
25 from 1 to 18 carbon atoms, said optionally substituted unsaturated acyl and optionally substituted saturated acyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;
30 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of succinic acid anhydride, glutaric acid anhydride and acetic acid anhydride, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy and cyano;

5 separating and isolating said compound of Formula III or salts thereof.

In a 41st embodiment, the invention is represented by the process to manufacture a compound of Formula V or salts thereof



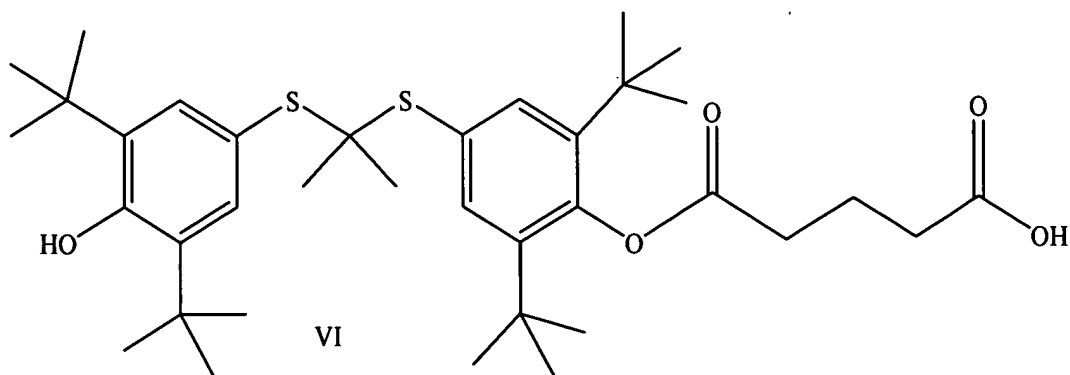
10 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium; Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

15 reacting said magnesium salt with succinic acid anhydride;

separating and isolating said compound of Formula V or salts thereof.

In a 42nd embodiment, the invention is represented by the process to manufacture a compound of Formula VI or salts thereof



comprising:

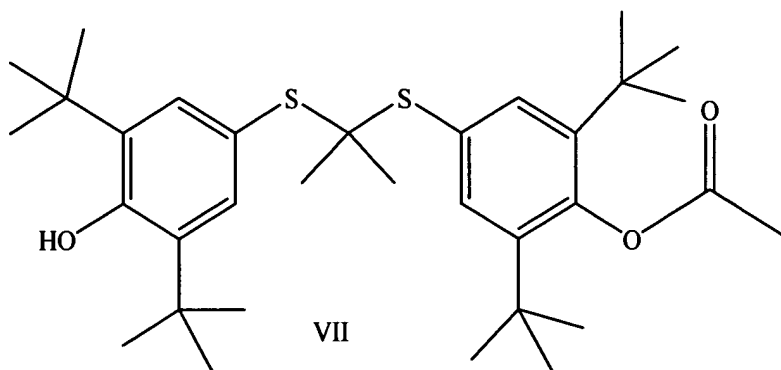
reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;

5 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with glutaric acid anhydride;

separating and isolating said compound of Formula VI or salts thereof.

In a 43rd embodiment, the invention is represented by the process to manufacture
10 a compound of Formula VII or salts thereof



comprising:

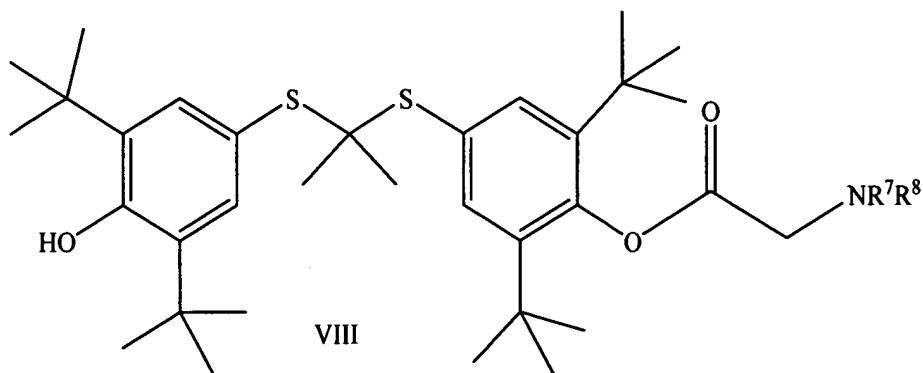
reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;

15 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with acetic acid anhydride;

separating and isolating said compound of Formula VII or salts thereof.

In a 44th embodiment, the invention is represented by the process to manufacture a compound of Formula VIII or salts thereof



wherein R⁷ and R⁸ are independently selected from the group consisting of hydrogen,
 5 acyl, alkyl, alkenyl, aryl, aralkyl, Si(alkyl)₃, protected carboxy, alkylsulfonyl, and
 arylsulfonyl

comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
 consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium; :

10 Diethylmagnesium

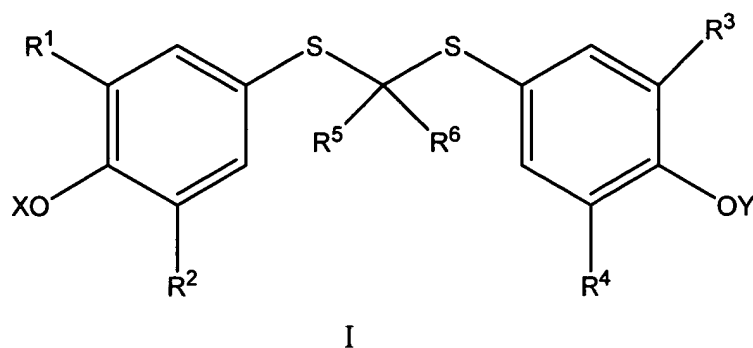
and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with acetic acid anhydride substituted by a protected or
 unprotected amino;

separating and isolating said compound of Formula VIII or salts thereof

15

In a 45th embodiment, the invention is represented by the process to manufacture a compound of Formula I or salts thereof



20

wherein R^1 , R^2 , R^3 , and R^4 are independently selected from the group consisting of hydrogen and alkyl, said alkyl optionally substituted by hydroxy, alkyl, alkenyl, acyl, nitro, amino, halo, carboxy and cyano;

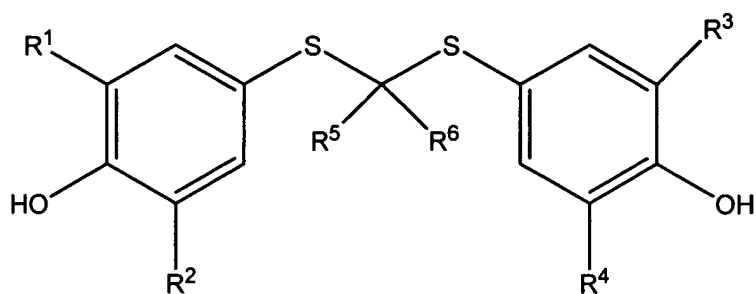
R^5 and R^6 are the same or different and independently selected from the group consisting of alkyl, alkenyl, and aryl all of which can be optionally substituted by hydroxy, alkyl, alkenyl, acyl, nitro, amino, halo, carboxy and cyano;

R^5 and R^6 can come together to form a carbocyclic ring; X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

comprising:

reacting a compound of Formula II



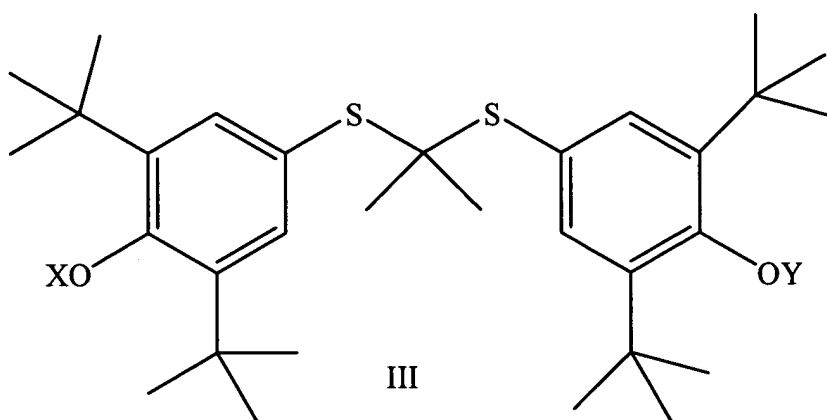
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wherein R^1 , R^2 , R^3 , R^4 , R^5 and R^6 are as previously defined, with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be

substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula I or salts thereof.

- 5 In a 46th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof

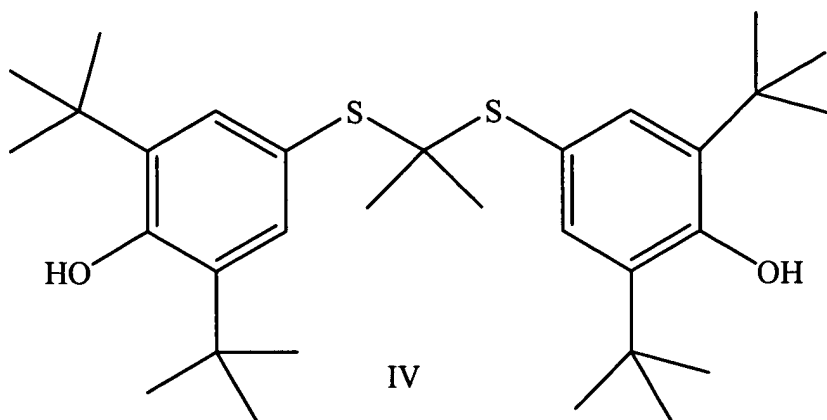


wherein:

- X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
- 10

- Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
- 15
- comprising:

reacting a compound of Formula IV



with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium, alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

5 reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

10 separating and isolating said compound of Formula III or salts thereof.

In a 47th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

20 comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt or a reagent selected from the group consisting of an alkyl lithium, alkenyl lithium,

alkynyl lithium, aryl lithium, aralkyl lithium, and a heteroaryl lithium, all which can be optionally substituted to form a lithium salt;

reacting said magnesium salt or lithium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-

5 sulfonfyl alkyl, a saturated or unsaturated alkyl-O-sulfonfyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

10

In a 48th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is selected from the group consisting of hydrogen, an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl

15 having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having

20 from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of a

25 saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonfyl alkyl, a saturated or unsaturated alkyl-O-sulfonfyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

30 separating and isolating said compound of Formula III or salts thereof.

In a 49th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
5 having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally
substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;

10 reacting said magnesium salt with a compound selected from the group consisting of a
saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a
saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl,
and a saturated or unsaturated epoxide, all of which may optionally be substituted by one
or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl,
15 nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

In a 50th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

20 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally
substituted saturated alkyl optionally containing a polar or charged functionality;

25 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
consisting of alkylmagnesium halide, alkenylmagnesium halide, alkynylmagnesium
halide, arylmagnesium halide, arylalkylmagnesium halide, alkylmagnesium alkyl,
arylmagnesium aryl, arylalkynylmagnesium halide, arylalkenylmagnesium halide, and

30 heteroarylmagnesium halide, all of which may optionally be substituted by one or more

selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy, to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a
5 saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

10

In a 51st embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
15 having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from
20 the group consisting of alkylmagnesium halide, alkenylmagnesium halide, alkynylmagnesium halide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy, to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of
25 alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

30 separating and isolating said compound of Formula III or salts thereof.

In a 52nd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
5 having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

10 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of Methylmagnesium bromide; Octadecylmagnesium chloride; Tetradecylmagnesium chloride; n-Pentadecylmagnesium bromide; Ethynylmagnesium chloride; n-Nonylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentyl magnesium chloride; Cyclopropylmagnesium bromide; (1-Methyl-2-
15 propenyl)magnesium chloride; 1-Decylmagnesium bromide; 1-Octylmagnesium bromide; 1-Propynylmagnesium bromide; Dodecylmagnesium bromide; sec-Butylmagnesium chloride; 1-Propenylmagnesium bromide; Isopropenylmagnesium bromide; (2,2-Dimethylpropyl)magnesium chloride; 1-Heptylmagnesium bromide; 3-Butenylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium
20 chloride; (2-Methyl-2-propenyl)magnesium chloride; Ethynylmagnesium bromide; 1-Hexylmagnesium bromide; Vinylmagnesium chloride; Allylmagnesium chloride; Ethylmagnesium chloride; n-Propylmagnesium chloride; Vinylmagnesium bromide; Allylmagnesium bromide; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide; 1-Propylmagnesium
25 bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;

30 reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may

optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

separating and isolating said compound of Formula III or salts thereof.

5

In a 53rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
10 having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from
15 the group consisting of Methylmagnesium bromide; Octadecylmagnesium chloride; Tetradecylmagnesium chloride; n-Nonylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentyl magnesium chloride; Cyclopropylmagnesium bromide; 1-Decylmagnesium bromide; 1-Octylmagnesium bromide; Dodecylmagnesium bromide; sec-
20 Butylmagnesium chloride; (2,2-Dimethylpropyl)magnesium chloride; 1-Heptylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium chloride; 1-Hexylmagnesium bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide;
25 1-Propylmagnesium bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of
30 alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may

optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

separating and isolating said compound of Formula III or salts thereof.

5

In a 54th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
10 having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from
15 the group consisting of Methylmagnesium bromide; n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium bromide; Cyclopentylmagnesium bromide; tert-Pentylmagnesium chloride; Cyclopropylmagnesium bromide; 1-Octylmagnesium bromide; sec-Butylmagnesium chloride; (2,2-Dimethylpropyl)magnesium chloride; 1-Heptylmagnesium bromide; 1-Pentylmagnesium chloride; 2-Methylpropylmagnesium
20 chloride; 1-Hexylmagnesium bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride; Cyclohexylmagnesium bromide; 1-Propylmagnesium bromide; Isobutylmagnesium bromide; Ethylmagnesium bromide; 2-Butylmagnesium bromide; 2-Propylmagnesium bromide; Methylmagnesium iodide; n-Butylmagnesium
25 chloride; n-Butylmagnesium bromide; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may
30 optionally be substituted by one or more selected from the group consisting of protected

hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

5 In a 55th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
10 from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Octylmagnesium chloride; (2-Methylpropenyl)magnesium
15 bromide; Ethylmagnesium chloride; n-Propylmagnesium chloride; Isopropylmagnesium chloride; Isopropylmagnesium bromide; Cyclohexylmagnesium chloride;
Methylmagnesium iodide; n-Butylmagnesium chloride; tert-Butylmagnesium chloride; and Methylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of
20 alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
25 separating and isolating said compound of Formula III or salts thereof.

 In a 56th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

30 Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having

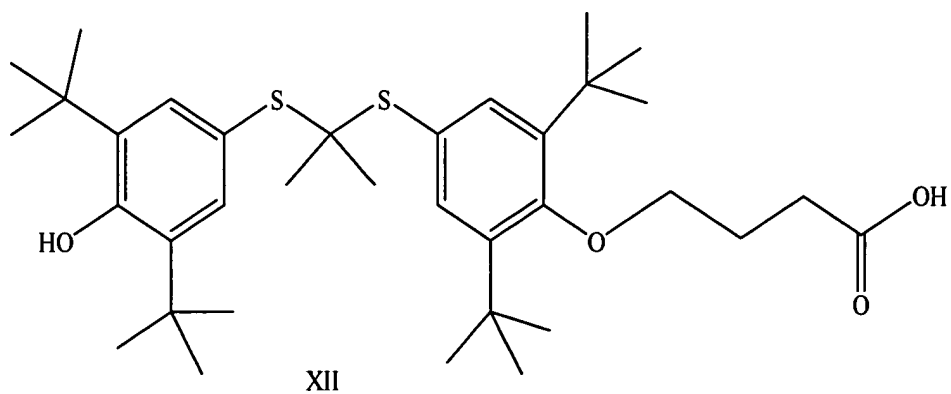
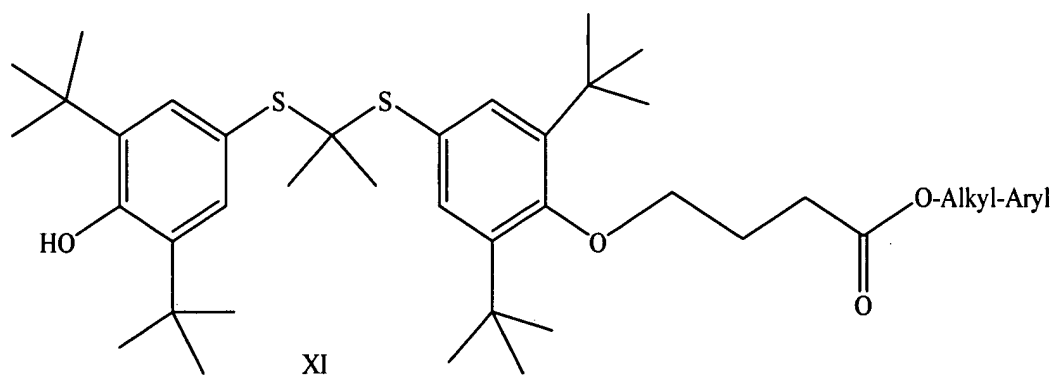
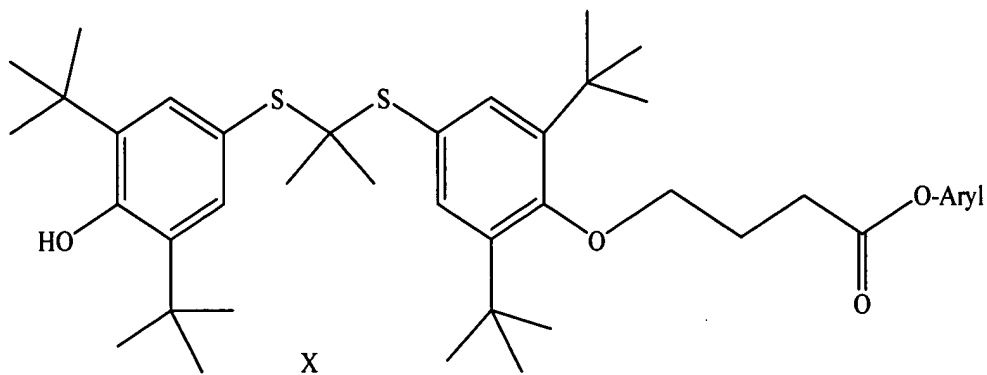
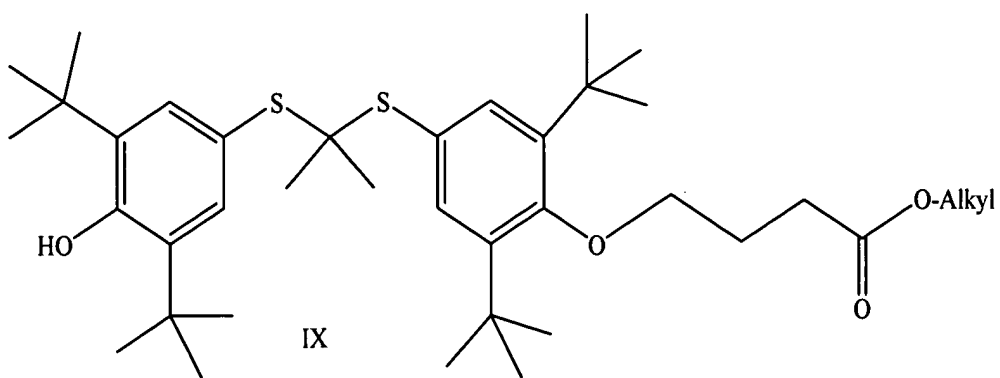
from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a solution of a compound of Formula IV with isopropylmagnesium chloride to
5 form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected
10 hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

separating and isolating said compound of Formula III or salts thereof.

In a 57th embodiment, the invention is represented by the process to manufacture
15 a compound of Formula IX, X, XI or XII or salts thereof

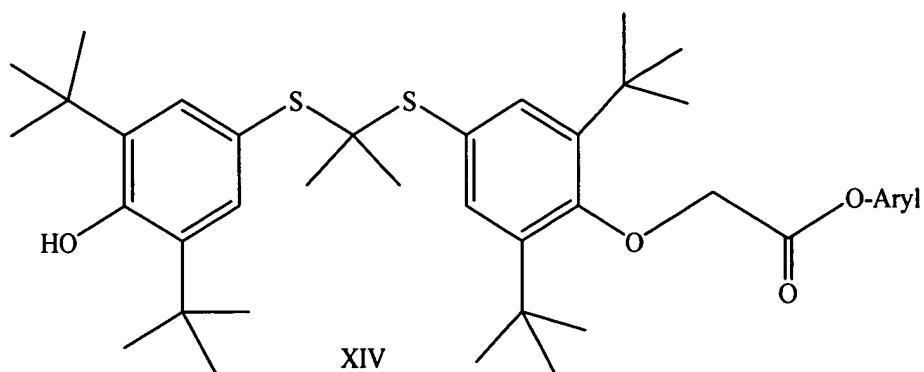
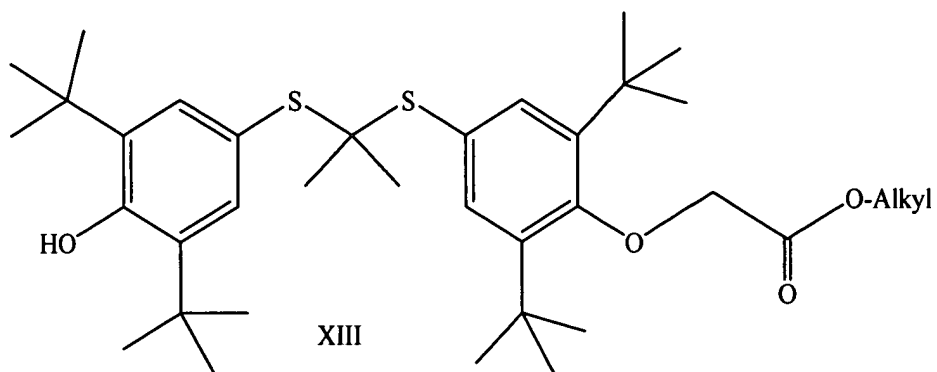


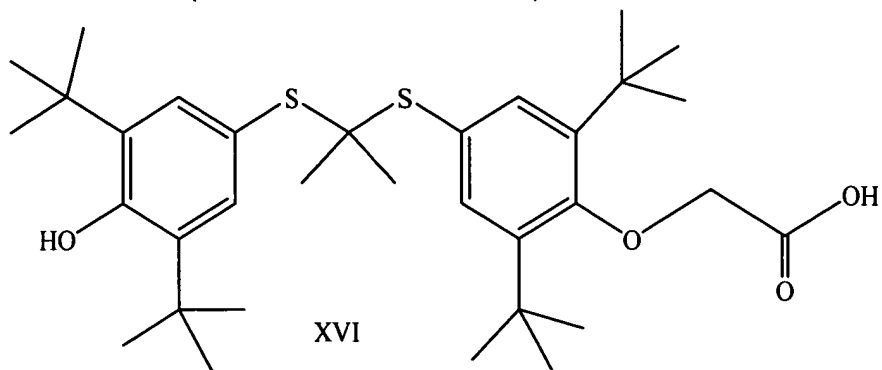
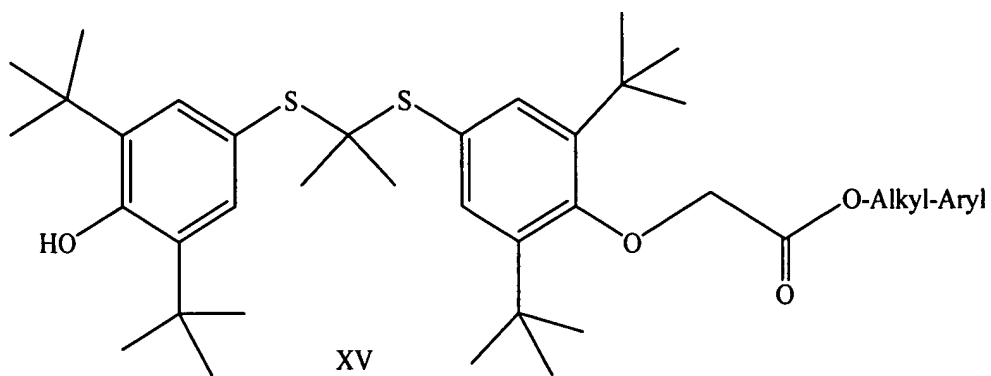
comprising:

reacting a solution of a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, and butyrolactone; separating and isolating said compound of Formula IX, X, XI or XII or salts thereof.

- 5 In a 58th embodiment, the invention is represented by the process to manufacture a compound of Formula XIII, XIV, XV or XVI or salts thereof





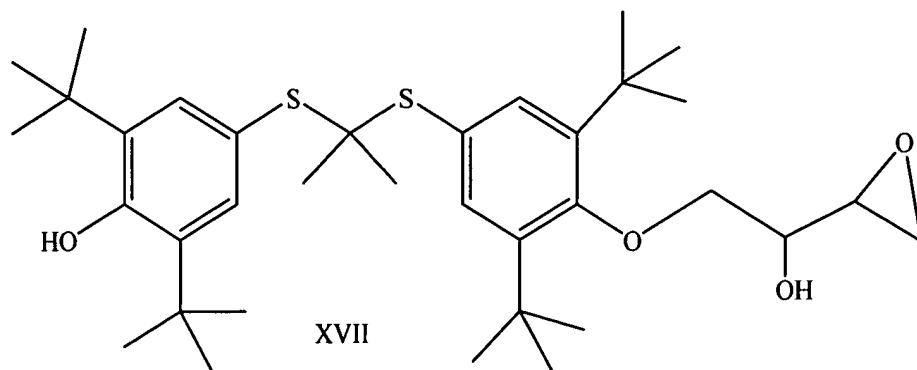
comprising:

reacting a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

- 5 reacting said magnesium salt with alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and alkali metal haloacetate;

separating and isolating said compound of Formula XIII, XIV, XV or XVI or salts thereof.

- 10 In a 59th embodiment, the invention is represented by the process to manufacture a compound of of Formula XVII or salts thereof



comprising:

reacting a compound of Formula IV with isopropylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with diepoxybutane;

5 separating and isolating said compound of Formula XVI or salts thereof.

In a 60th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

10 Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

comprising:

15 reacting a solution of a compound of Formula IV with a Grignard Reagent selected from arylmagnesium halide or heteroarylmagnesium halide to form a magnesium salt, wherein said arylmagnesium halide and heteroarylmagnesium halide may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;

20 reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide

25 and cyano;

separating and isolating said compound of Formula III or salts thereof.

In a 61st embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

30 X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

5 comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Chloro-4-fluorophenylmagnesium bromide; 3-Fluoro-2-

methylphenylmagnesium bromide; 5-Fluoro-2-methoxyphenylmagnesium bromide; 5-

Fluoro-2-methylphenylmagnesium bromide; 3,5-Dimethyl-4-methoxyphenylmagnesium

10 bromide; 3-Fluoro-4-methylphenylmagnesium bromide; 3-

[Bis(trimethylsilyl)amino]phenylmagnesium chloride; 3-Thienylmagnesium iodide; 3-

Fluoro-4-chlorophenylmagnesium bromide; 3,4,5-Trifluorophenylmagnesium bromide;

4-Methoxy-2-methylphenylmagnesium bromide; 2,4-Dimethoxyphenylmagnesium

bromide; 2,3-Dimethylphenylmagnesium bromide; 3-Methylphenylmagnesium chloride;

15 (4-methyl-1-naphthalenyl)magnesium bromide; (3-fluoro-4-methoxyphenyl)magnesium

bromide; 2-Chloro-5-thienylmagnesium bromide; 3,4-Dimethylphenylmagnesium

chloride; 3-Methyl-2-thienylmagnesium bromide; Pentamethylphenylmagnesium

bromide; 3,4-Dimethoxyphenylmagnesium bromide; (3,4-Dimethylphenyl)magnesium

bromide; (3,5-Dichlorophenyl)magnesium bromide; (4-Fluoro-3-

20 methylphenyl)magnesium bromide; 3,4-Dichlorophenylmagnesium bromide; 2,3,5,6-

Tetramethylphenylmagnesium bromide; 9-Phenanthryl magnesium bromide; (4-tert-

Butylphenyl)magnesium bromide; 2,5-Dimethoxyphenylmagnesium bromide; 3,5-

Difluorophenylmagnesium bromide; 4-Chlorophenylmagnesium chloride; (6-Methoxy-2-

naphthyl)magnesium bromide; (2-Methoxy-1-naphthyl)magnesium bromide; 3-

25 Methoxyphenylmagnesium bromide; (3-Chlorophenyl)magnesium bromide; (3,5-

Dimethylphenyl)magnesium bromide; (2-Methylphenyl)magnesium chloride; 4-Fluoro-2-

methylphenylmagnesium bromide; (2,5-Dimethylphenyl)magnesium bromide; m-

Methylphenylmagnesium bromide; 4-Ethylphenylmagnesium bromide; 2-

Pyridylmagnesium bromide; 4-Phenoxyphenylmagnesium bromide; 2-

30 Naphthylmagnesium bromide; (2-Methyl-1-naphthyl)magnesium bromide; 2,6-

Dimethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; 4-

(Methylthio)phenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; 3,4-Methylenedioxyphenylmagnesium bromide; 3-Fluorophenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; 4-(Dimethylamino)phenylmagnesium bromide; 2-Thienylmagnesium bromide; (4-Methylphenyl)magnesium bromide; Mesitylmagnesium bromide; 2-Tolylmagnesium bromide; Pentafluorophenylmagnesium bromide; (4-Chlorophenyl)magnesium bromide; 1-Naphthalenylmagnesium bromide; 4-Methylphenylmagnesium chloride; 4-Fluorophenylmagnesium bromide; Phenylmagnesium chloride; Phenylmagnesium bromide; and (4-Biphenyl)l)magnesium bromide to form a magnesium salt;
10 reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected
15 hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

In a 62nd embodiment, the invention is represented by the process to manufacture
20 a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally
25 substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3,5-Dimethyl-4-methoxyphenylmagnesium bromide; 4-Methoxy-2-methylphenylmagnesium bromide; 2,4-Dimethoxyphenylmagnesium bromide; 2,3-Dimethylphenylmagnesium bromide; 3-Methylphenylmagnesium chloride; 3,4-Dimethylphenylmagnesium chloride; Pentamethylphenylmagnesium bromide; 3,4-
30 Dimethylphenylmagnesium chloride; 3,4-

Dimethoxyphenylmagnesium bromide; (3,4-Dimethylphenyl)magnesium bromide; 2,3,5,6-Tetramethylphenylmagnesium bromide; (4-tert-Butylphenyl)magnesium bromide; 2,5-Dimethoxyphenylmagnesium bromide; 3-Methoxyphenylmagnesium bromide; (3,5-Dimethylphenyl)magnesium bromide; (2-Methylphenyl)magnesium chloride; (2,5-Dimethylphenyl)magnesium bromide; m-Methylphenylmagnesium bromide; 4-Ethylphenylmagnesium bromide; 4-Phenoxyphenylmagnesium bromide; 2,6-Dimethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; 3,4-Methylenedioxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; Mesitylmagnesium bromide; 2-Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium chloride; and Phenylmagnesium bromide to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;

separating and isolating said compound of Formula III or salts thereof.

In a 63rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methylphenylmagnesium chloride; (4-tert-Butylphenyl)magnesium

bromide; 3-Methoxyphenylmagnesium bromide; (2-Methylphenyl)magnesium chloride; m-Methylphenylmagnesium bromide; 4-Ethylphenylmagnesium bromide; 2-Ethylphenylmagnesium bromide; (4-Isopropylphenyl)magnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; 2-Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium chloride; and Phenylmagnesium bromide to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

15

In a 64th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methylphenylmagnesium chloride; 3-Methoxyphenylmagnesium bromide; (2-Methylphenyl)magnesium chloride; m-Methylphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; Phenylmagnesium iodide; (4-Methoxyphenyl)magnesium bromide; (4-Methylphenyl)magnesium bromide; 2-Tolylmagnesium bromide; 4-Methylphenylmagnesium chloride; Phenylmagnesium chloride; and Phenylmagnesium bromide to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

In a 65th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

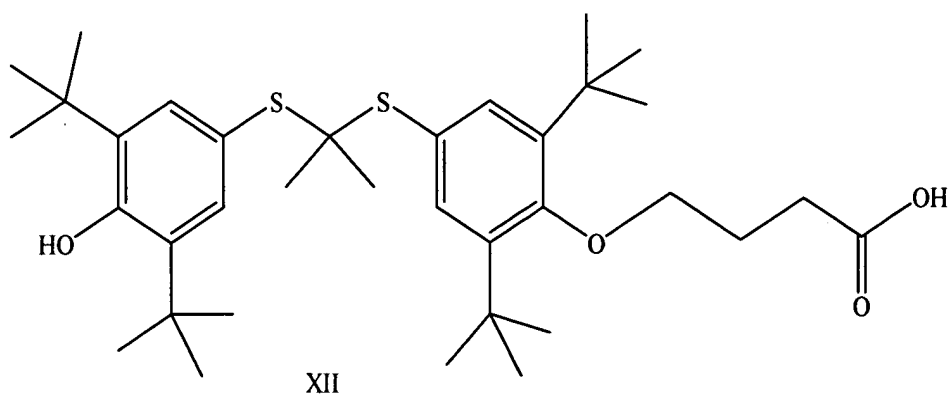
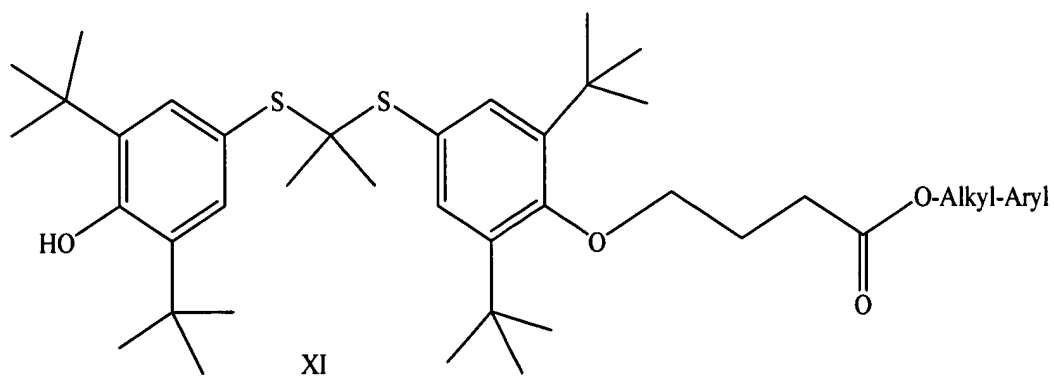
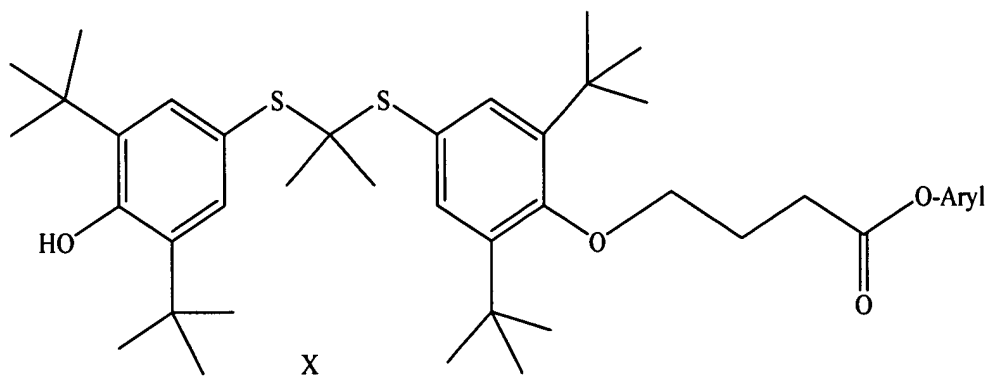
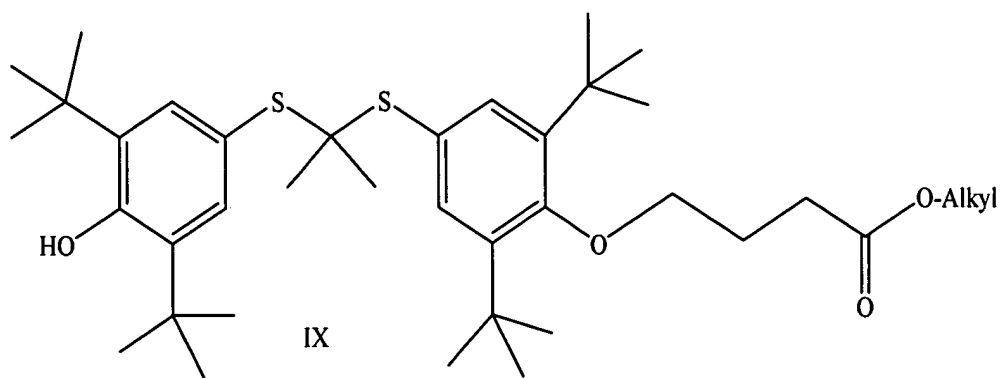
In a 66th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;

- 5 comprising:
- reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
- reacting said magnesium salt with a compound selected from the group consisting of
- 10 alkyl 4-halobutyrate, aryl 4-halobutrate, aralkyl 4-halobutyrate, butyrolactone, alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and diepoxybutane, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
- 15 separating and isolating said compound of Formula III or salts thereof.

In a 67th embodiment, the invention is represented by the process to manufacture a compound of Formula IX, X, XI or XII or salts thereof

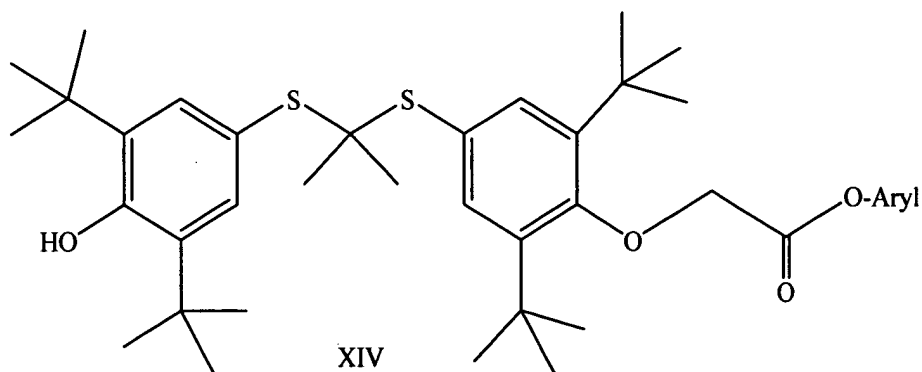
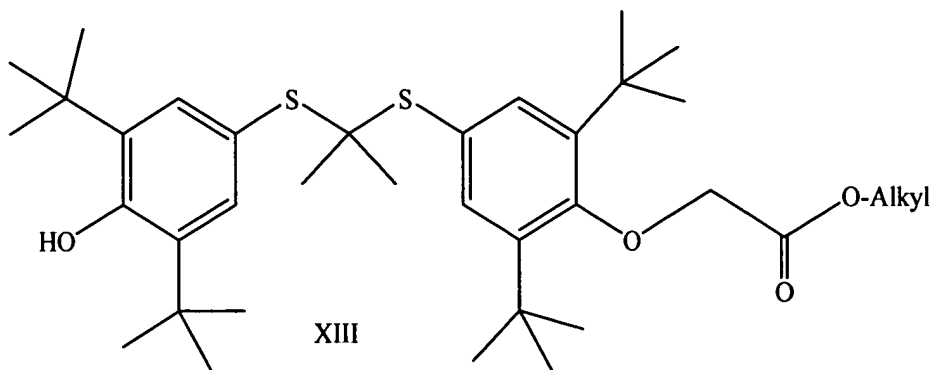


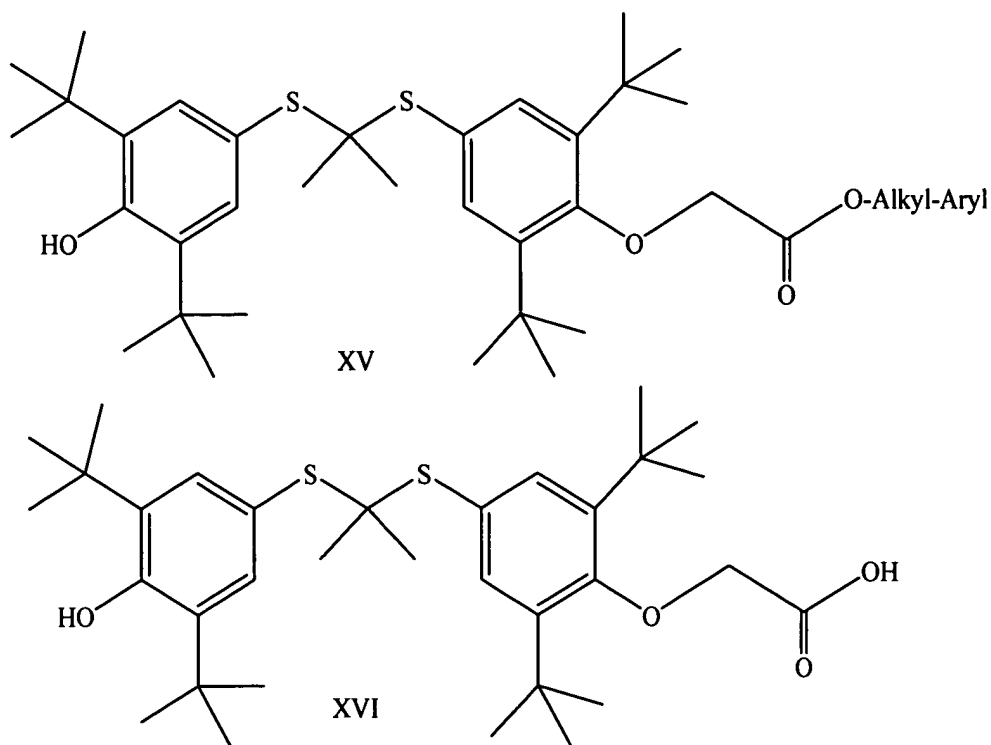
comprising:

reacting a solution of a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; o-

- Methoxyphenyl)magnesium bromide; and Phenylmagnesium chloride to form a magnesium salt;
reacting said magnesium salt with a compound from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, and butyrolactone;
5 separating and isolating said compound of Formula IX, X, XI or XII or salts thereof.

In a 68th embodiment, the invention is represented by the process to manufacture a compound of Formula XIII, XIV, XV or XVI or salts thereof





comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium

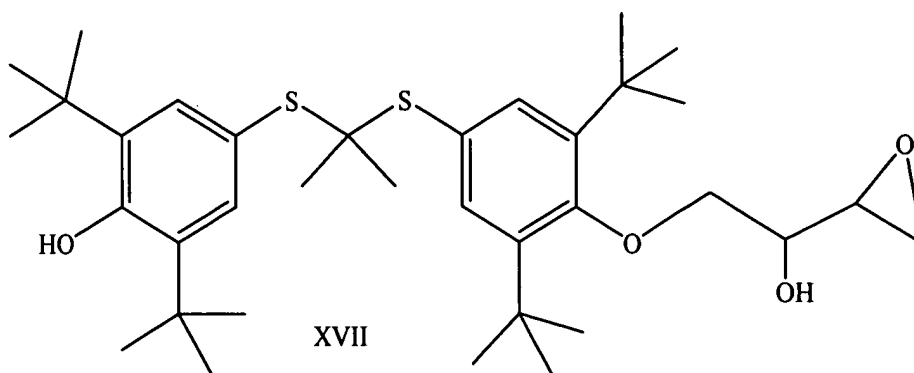
5 bromide; and Phenylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and alkali metal haloacetate;

separating and isolating said compound of Formula XIII, XIV, XV or XVI or salts thereof.

10

In a 69th embodiment, the invention is represented by the process to manufacture a compound of Formula XVII or salts thereof



comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 3-Methoxyphenylmagnesium bromide; (o-Methoxyphenyl)magnesium

5 bromide; and Phenylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with diepoxybutane;

separating and isolating said compound of Formula XVII or salts thereof.

In a 70th embodiment, the invention is represented by the process to manufacture
10 a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl
having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally
15 substituted saturated alkyl optionally containing a polar or charged functionality;

comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group
consisting of arylalkylmagnesium halide, arylalkynylmagnesium halide, and
arylalkenylmagnesium halide to form a magnesium salt, all of which may optionally be
20 substituted by one or more selected from the group consisting of protected hydroxy,
alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;

reacting said magnesium salt with a compound selected from the group consisting of a
saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a
saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl,

25 and a saturated or unsaturated epoxide, all of which may optionally be substituted by one

or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

5 In a 71st embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
10 from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 2,5-Dimethylbenzylmagnesium chloride; 2,6-Dichlorobenzylmagnesium
15 chloride; 2,4-Dichlorobenzylmagnesium chloride; 2-Fluorobenzylmagnesium chloride; 2,4-Dimethylbenzylmagnesium chloride; 3-Bromobenzylmagnesium bromide; 4-Bromobenzylmagnesium bromide; (2-Phenylethyl)magnesium chloride; 3-Fluorobenzylmagnesium chloride; (3,4-Dichlorobenzyl)magnesium chloride; 2-Bromobenzylmagnesium bromide; 4-Methoxybenzylmagnesium chloride; 4-Methylbenzylmagnesium chloride; m-Methylbenzylmagnesium chloride; 2-Methylbenzylmagnesium chloride; 3-Chlorobenzylmagnesium chloride; 2-Chlorobenzylmagnesium chloride; m-Methoxybenzylmagnesium chloride; Benzylmagnesium chloride; (Phenylethynyl)magnesium bromide; 4-Fluorobenzylmagnesium chloride; Benzylmagnesium bromide; 4-
20 Chlorobenzylmagnesium chloride; and 2-Chloro-6-fluorobenzylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl,
30 and a saturated or unsaturated epoxide, all of which may optionally be substituted by one

or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

5 In a 72nd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
10 from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of 2,5-Dimethylbenzylmagnesium chloride; 2,4-Dimethylbenzylmagnesium
15 chloride; (2-Phenylethyl)magnesium chloride; 4-Methoxybenzylmagnesium chloride; 4-Methylbenzylmagnesium chloride; m-Methylbenzylmagnesium chloride; 2-Methylbenzylmagnesium chloride; m-Methoxybenzylmagnesium chloride; Benzylmagnesium chloride; and Benzylmagnesium bromide to form a magnesium salt; reacting said magnesium salt with a compound selected from the group consisting of a
20 saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
25 separating and isolating said compound of Formula III or salts thereof.

 In a 73rd embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

30 Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having

from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality; comprising:

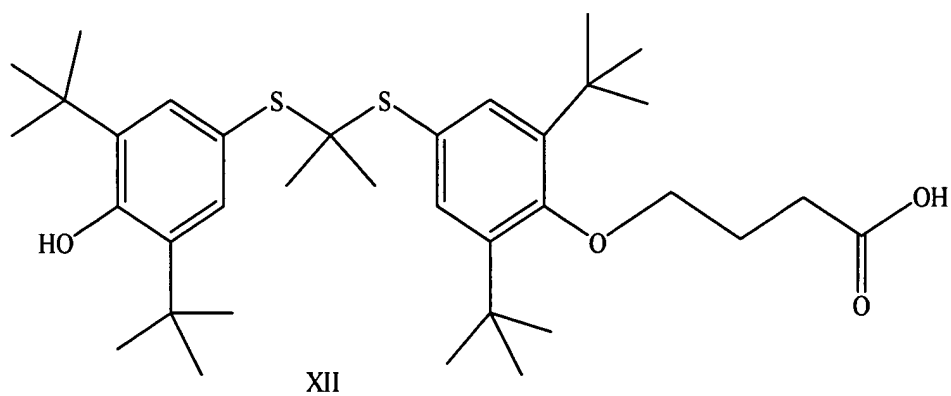
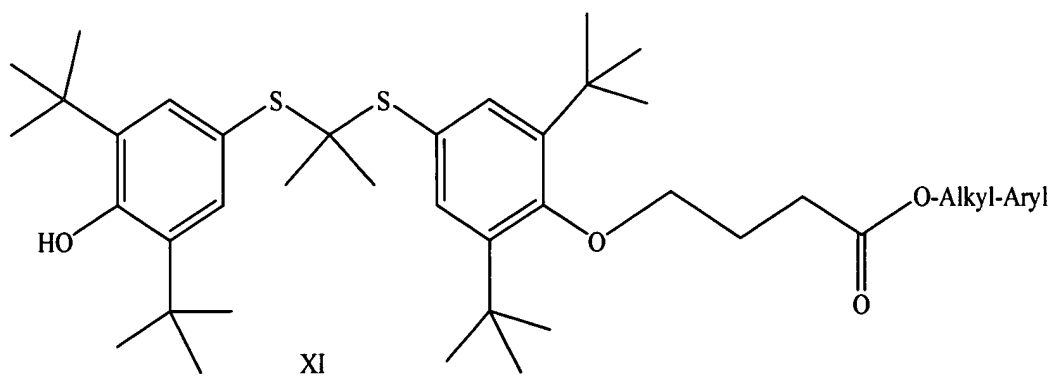
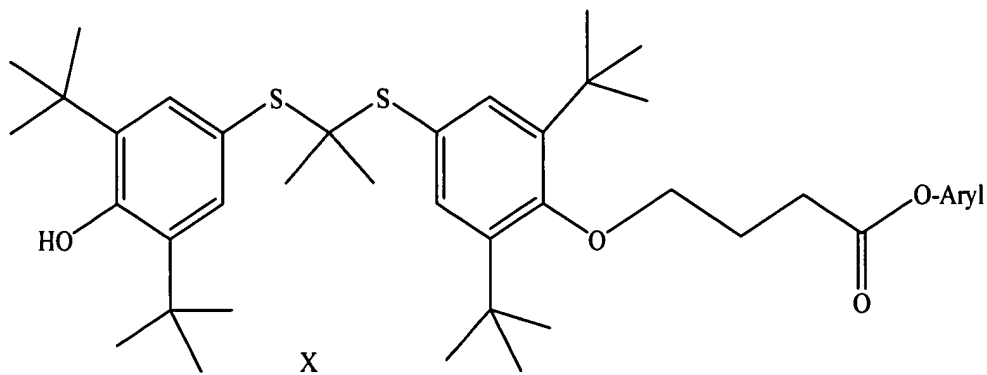
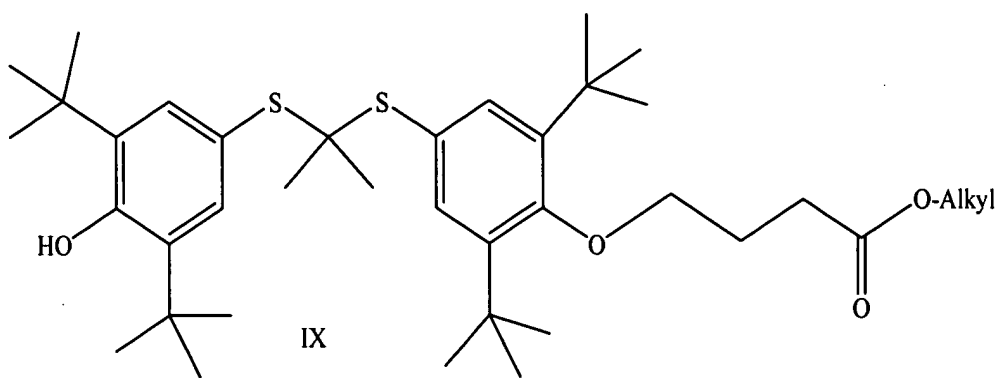
reacting a compound of Formula IV with Benzylmagnesium chloride to form a

5 magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one
10 or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

In a 74th embodiment, the invention is represented by the process to manufacture

15 a compound of Formula IX, X, XI or XII or salts thereof

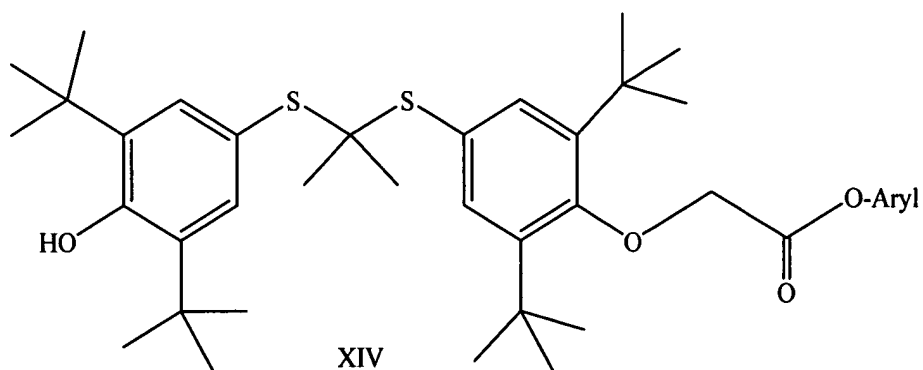
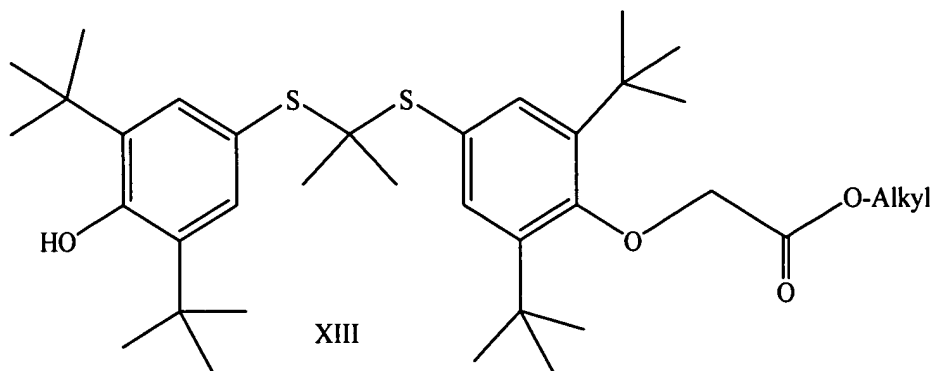


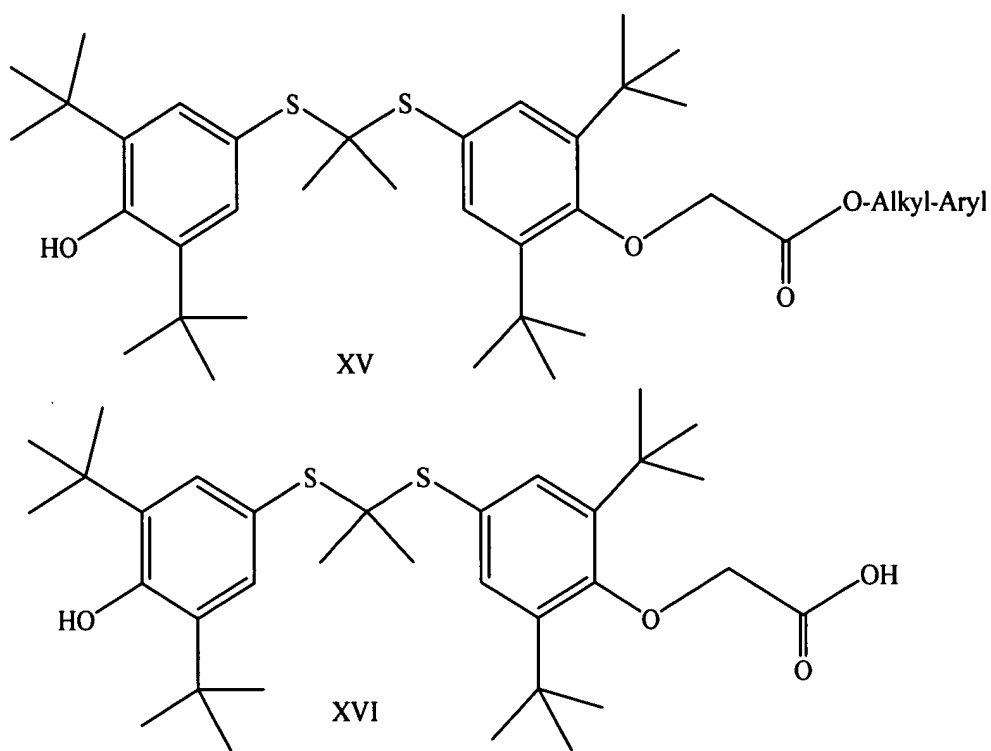
comprising:

reacting a solution of a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of alkyl 4-halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate and butyrolactone; separating and isolating said compound of Formula IX, X, XI or XII or salts thereof.

- 5 In a 75th embodiment, the invention is represented by the process to manufacture a compound of Formula XIII, XIV, XV or XVI or salts thereof





comprising:

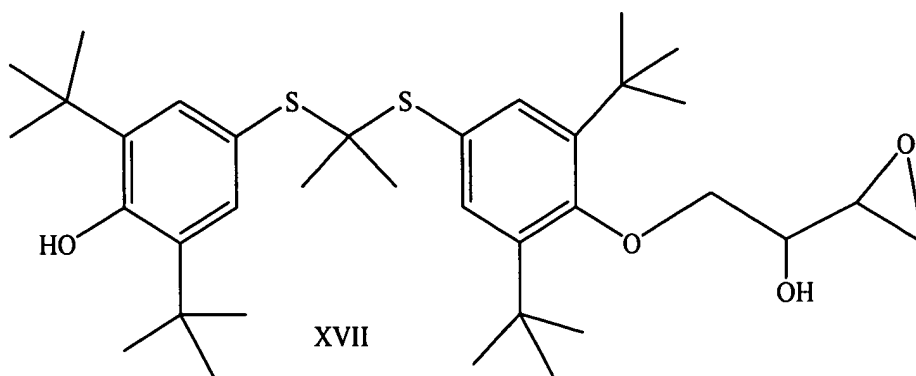
reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

- 5 reacting said magnesium salt with alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and alkali metal haloacetate;

separating and isolating said compound of Formula XIII, XIV, XV or XVI or salts thereof.

10

In a 76th embodiment, the invention is represented by the process to manufacture a compound of Formula XVII or salts thereof



comprising:

reacting a compound of Formula IV with Benzylmagnesium chloride to form a magnesium salt;

- 5 reacting said magnesium salt with diepoxybutane;
- separating and isolating said compound of Formula XVII or salts thereof.

In a 77th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

- 10 X is hydrogen;
- Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
- 15 comprising:
 - reacting a compound of Formula IV with a Grignard Reagent selected from alkylmagnesium alkyl or arylmagnesium aryl to form a magnesium salt, wherein said alkylmagnesium alkyl and arylmagnesium aryl may optionally be substituted by one or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, protected acyl, nitro, protected amino, halo and protected carboxy;
 - 20 reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one

or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano; separating and isolating said compound of Formula III or salts thereof.

5 In a 78th embodiment, the invention is represented by the process to manufacture a compound of Formula III or salts thereof wherein:

X is hydrogen;

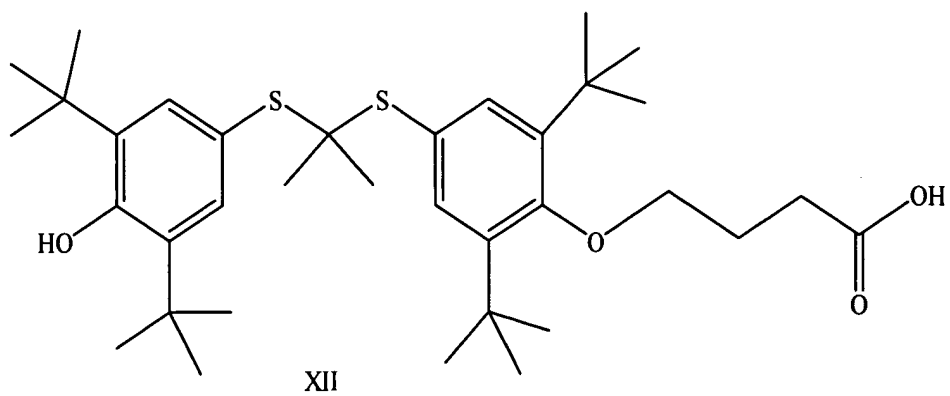
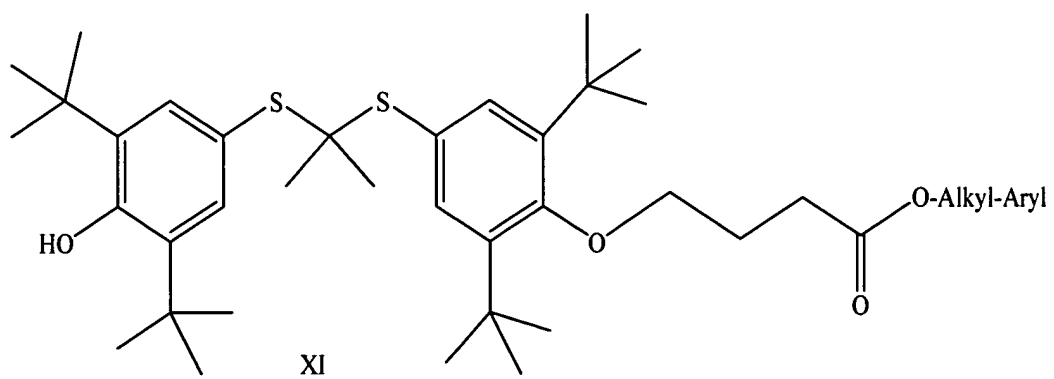
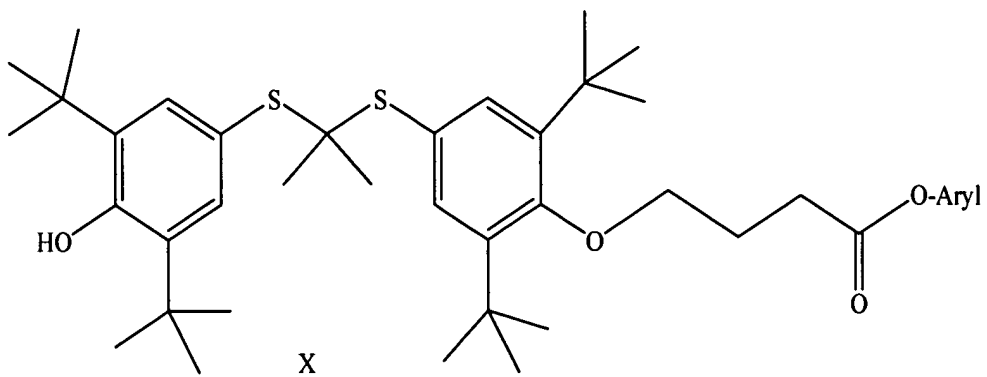
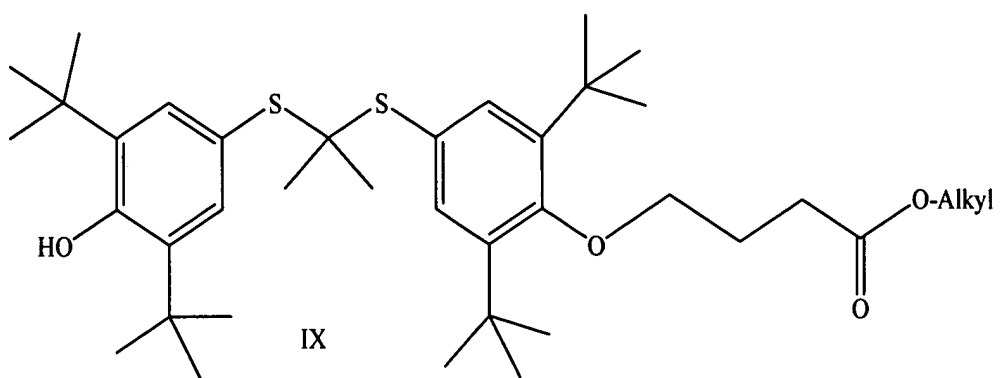
Y is selected from the group consisting of an optionally substituted unsaturated alkyl having from 1 to 10 carbon atoms, and an optionally substituted saturated alkyl having
10 from 1 to 10 carbon atoms, said optionally substituted unsaturated alkyl and optionally substituted saturated alkyl optionally containing a polar or charged functionality;
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;

15 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with a compound selected from the group consisting of a saturated or unsaturated alkyl halide, saturated or unsaturated alkyl-O-sulfonyl alkyl, a saturated or unsaturated alkyl-O-sulfonyl aryl, a saturated or unsaturated alkyl-O-acyl, and a saturated or unsaturated epoxide, all of which may optionally be substituted by one
20 or more selected from the group consisting of protected hydroxy, alkyl, alkenyl, acyl, nitro, protected amino, halo, protected carboxy, epoxide and cyano;
separating and isolating said compound of Formula III or salts thereof.

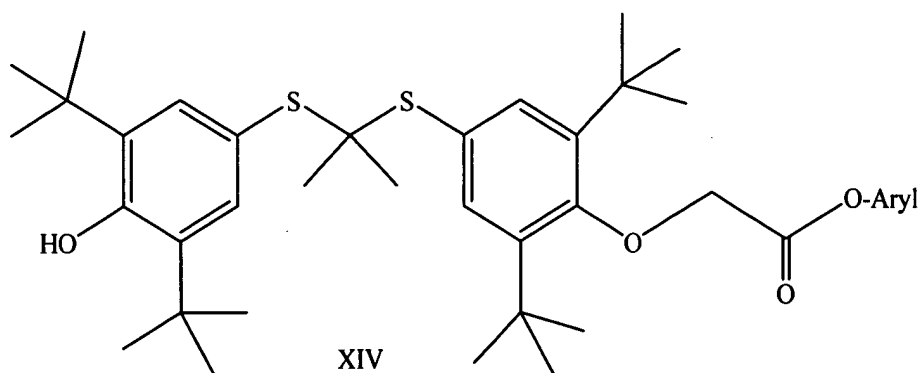
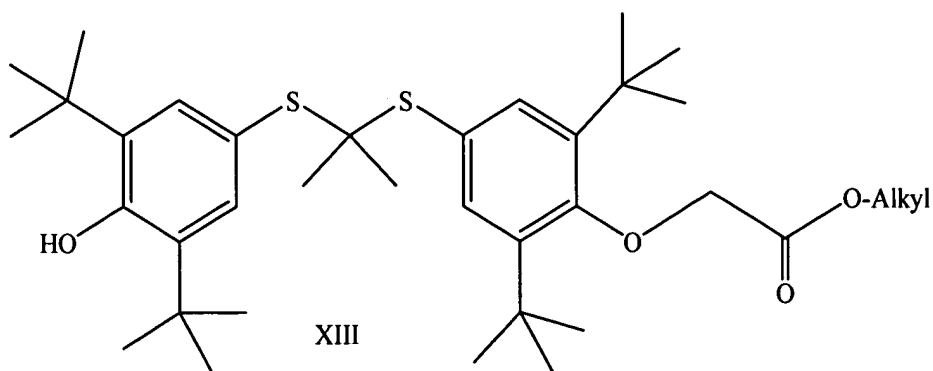
 In an 79th embodiment, the invention is represented by the process to manufacture
25 a compound of Formula IX, X, XI or XII or salts thereof

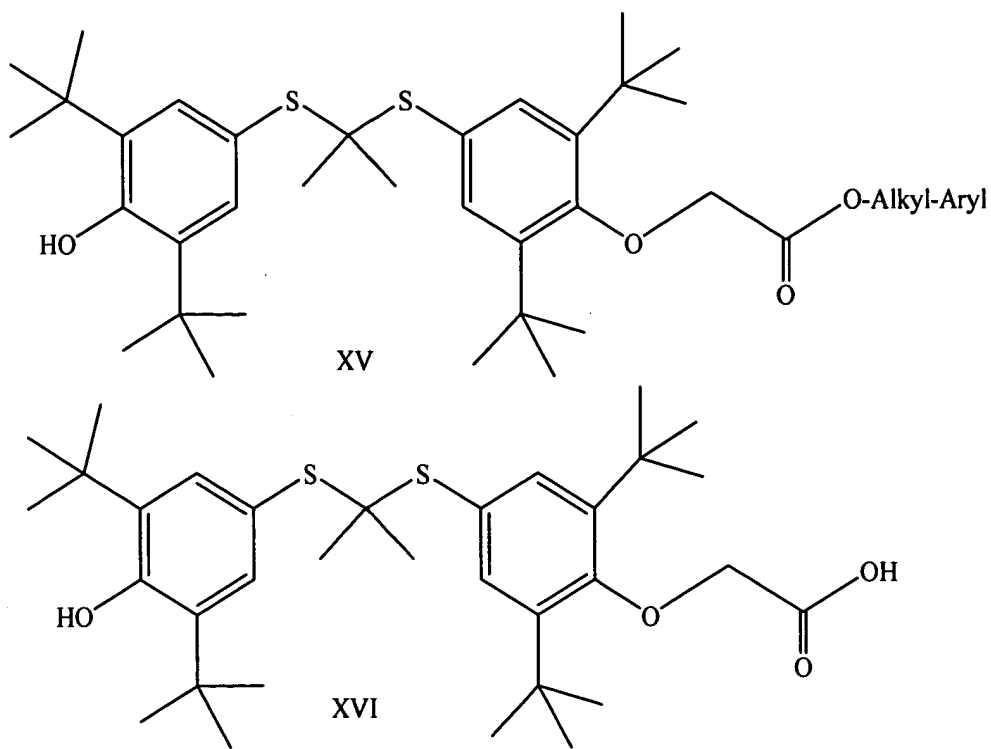


comprising:

- reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium; Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;
- reacting said magnesium salt with a compound from the group consisting of alkyl 4-
- 5 halobutyrate, aryl 4-halobutyrate, aralkyl 4-halobutyrate, and butyrolactone;
- separating and isolating said compound of Formula IX, X, XI or XII or salts thereof.

- In an 80st embodiment, the invention is represented by the process to manufacture
- 10 a compound of Formula XIII, XIV, XV or XVI or salts thereof





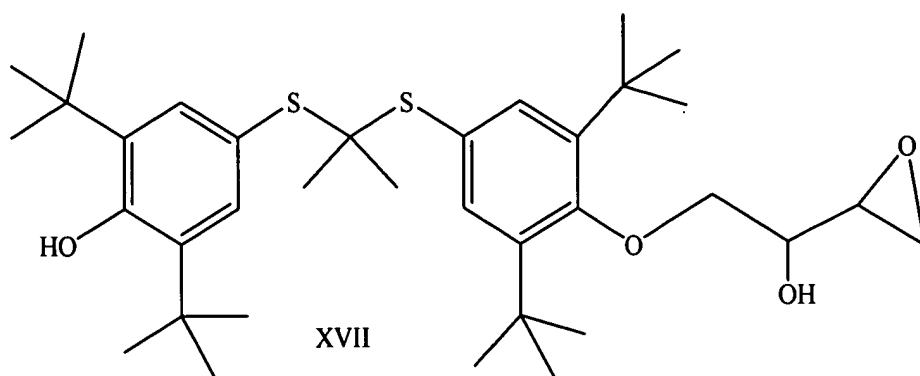
comprising:

reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;
 5 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;
 reacting said magnesium salt with alkyl haloacetate, aryl haloacetate, aralkyl haloacetate, and alkali metal haloacetate;

separating and isolating said compound of Formula XIII, XIV, XV or XVI or salts

10 thereof.

In an 81nd embodiment, the invention is represented by the process to manufacture a compound of Formula XVII or salts thereof



comprising:

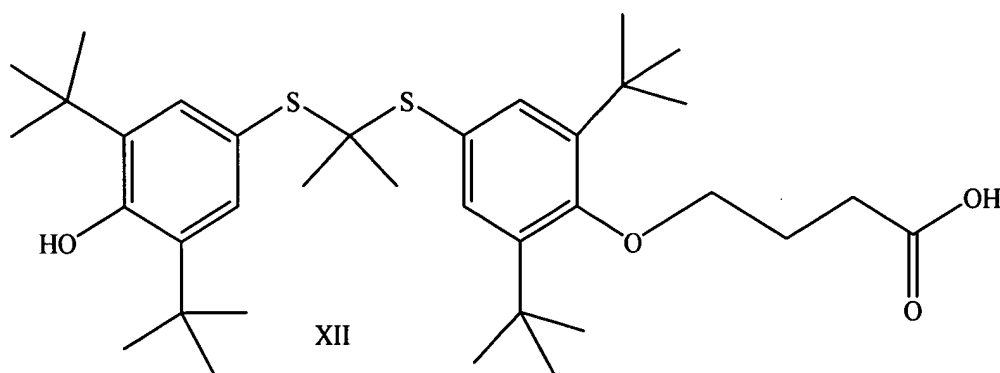
reacting a compound of Formula IV with a Grignard Reagent selected from the group consisting of n-Butyl-sec-butylmagnesium; Dimethylmagnesium; Di-n-Butylmagnesium;

5 Diethylmagnesium; and Diphenylmagnesium to form a magnesium salt;

reacting said magnesium salt with diepoxybutane;

separating and isolating said compound of Formula XVII or salts thereof.

10 In an 82nd embodiment, the invention is represented by the process to manufacture a compound of Formula XII or salts thereof



comprising:

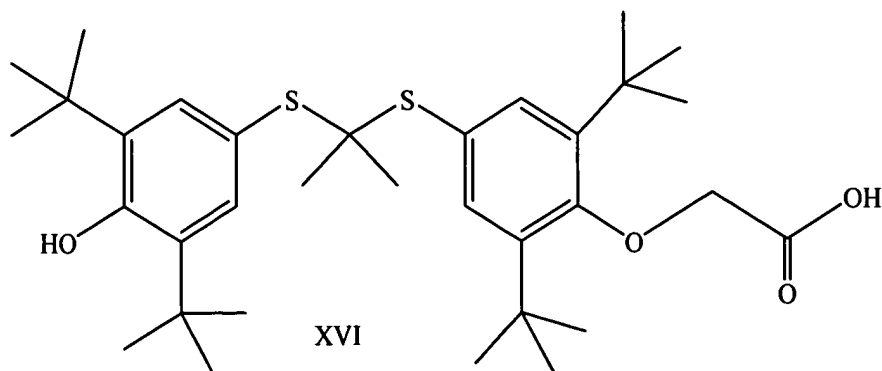
reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;

15 reacting said magnesium salt with alkyl haloacetate, aryl haloacetate or aralkyl haloacetate to form the compound of IX, X or XI;

hydrolyzing said compound of IX, X or XI;

separating and isolating said compound of Formula XII or salts thereof.

In an 83rd embodiment, the invention is represented by the process to manufacture a compound of Formula XVI or salts thereof



- 5 comprising:
reacting a compound of Formula IV with a Grignard Reagent to form a magnesium salt;
reacting said magnesium salt with alkyl haloacetate, aryl haloacetate, or aralkyl
haloacetate to form the compound of XIII, XIV or XV;
hydrolyzing said compound of XIII, XIV or XV;
10 separating and isolating said compound of Formula XVI or salts thereof.

DEFINITIONS

- The terms “alkyl” or “alk”, alone or in combination, unless otherwise specified,
15 includes a saturated straight, branched or cyclic primary, secondary, or tertiary
hydrocarbon from 1 to 18 carbon atoms and specifically includes methyl, ethyl, propyl,
isopropyl, cyclopropyl, butyl, isobutyl, *t*-butyl, pentyl, cyclopentyl, isopentyl, neopentyl,
hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and
2,3-dimethylbutyl, trifluoromethyl and perfluoroalkyl. The term includes both substituted
20 and unsubstituted alkyl groups. The alkyl group can be substituted with any moiety that
does not adversely affect the properties of the active compound, for example, but not
limited to hydroxyl, halo (including independently F, Cl, Br, and I), perfluoro alkyl
including trifluoromethyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano,
acyl, amido, carboxamido, carboxylate, thiol, alkylthio, azido, sulfonic acid, sulfate,
25 phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as

necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference. In one embodiment, the alkyl can be, for example, CF₃, CH₂CF₃, CCl₃, or cyclopropyl.

5 In the text, whenever the term C(alkyl range) is used, the term independently includes each member of that class as if specifically and separately set out. As a non-limiting example, the term "C₁₋₁₀" independently represents each species that falls within the scope, including, but not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, iso-butyl, tert-butyl, pentyl, iso-pentyl, neo-pentyl, cyclopentyl, cyclopentyl, hexyl, 1-
10 methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-ethylbutyl, 2-ethylbutyl, 3-ethylbutyl, 4-ethyl butyl, cyclohexyl, heptyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 6-methylhexyl, 1-ethylpentyl, 2-ethylpentyl, 3-ethylpentyl, 4-ethylpentyl, 5-ethylpenyl, 1-propylbutyl, 2-propylbutyl, 3-propylbutyl, 4-propylbutyl, cycloheptyl, octyl, 1-methylheptyl, 2-methylheptyl, 3-
15 methylheptyl, 4-methylheptyl, 5-methylheptyl, 6-methylheptyl, 7-methylheptyl, 1-ethylhexyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 5-ethylhexyl, 6-ethylhexyl, 1-propylpentyl, 2-propylpentyl, 3-propylpentyl, 4-propylpentyl, 5-propylpentyl, cyclooctyl, nonyl, cyclononyl, decyl, or cyclodecyl. C₁₋₆, C₁₋₈, C₂₋₈, C₃₋₈, C₁₋₁₀ and C₁₋₁₈ likewise can independently include any of its member groups, as if each were independently named
20 herein

 The term "**alkenyl**", alone or in combination, unless otherwise specified includes a straight, branched or cyclic hydrocarbon having from 2 to 10 carbon atoms and containing one or more double carbon-carbon bonds. Examples of such radicals are methylene, ethylene, methylethylene, and isopropylidene. Included within the scope of
25 this term are 1,2-ethane-diyl, 1,1-ethane-diyl, 1,3-propane-diyl, 1,2-propane-diyl, 1,3-butane-diyl, 1,4-butane-diyl and the like. The alkylene group or other divalent moiety disclosed herein can be optionally substituted with one or more moieties selected from the group consisting of alkyl, halo, haloalkyl, hydroxyl, carboxyl, acyl, acyloxy, amino, amido, carboxyl derivatives, alkylamino, dialkylamino, arylamino, alkoxy, aryloxy, nitro,
30 cyano, sulfonic acid, thiol, imine, sulfonyl, sulfanyl, sulfinyl, sulfamonyl, ester, carboxylic acid, amide, phosphonyl, phosphinyl, phosphoryl, phosphine, thioester,

thioether, acid halide, anhydride, oxime, hydrozine, carbamate, phosphonic acid, phosphonate, or any other viable functional group that does not inhibit the pharmacological activity of this compound, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective
5 Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

The term “**alkynyl**” includes an unsaturated, acyclic hydrocarbon radical, linear or branched, in so much as it contains one or more triple bonds, including such radicals containing about 2 to 10 carbon atoms or having from 2 to 6 carbon atoms. Said alkynyl
10 radicals may be optionally substituted with groups as defined below. Examples of suitable alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, pentyn-2-yl, 4-methoxypentyn-2-yl, 3-methylbutyn-1-yl, hexyn-1-yl, hexyn-2-yl, hexyn-3-yl, 3,3-dimethylbutyn-1-yl radicals and the like.

The term “**aryl**” or “**ar**”, alone or in combination, means a carbocyclic aromatic
15 system containing one, two or three rings wherein such rings may be attached together in a pendent manner or may be fused. The term “**aryl**” also includes an “**aryl**” optionally substituted with one or more of the moieties selected from the group consisting of alkyl, alkenyl, and alkynyl, alkoxy, aryloxy, halo, and amino.

The term “**acyl**”, alone or in combination, refers to a group of the formula
20 $C(O)R'$, wherein R' is hydrogen, alkyl, alkenyl, alkynyl, aryl, or aralkyl group. Examples of “acyl” are formyl, acetyl, benzoyl, trifluoroacetyl, phthaloyl, malonyl, nicotiny, and the like.

The term “**amino**”, alone or in combination, refers to the radical $-NH_2$ or $-NH-$,
or $-N-$.

25 The term “**alkoxy**”, alone or in combination, refers to an alkyl group as defined herein bonded through an oxygen linkage. Examples of alkoxys include methoxy, ethoxy, propoxy, butoxy, isopropoxy and tert-butoxy alkyls.

The term “**aryloxy**”, alone or in combination, refers to an aryl group as defined herein bonded through an oxygen linkage.

30 The term “**alkthio**”, alone or in combination, refers to an alkyl group as defined herein bonded through a sulfur linkage.

The term “**carboxy**”, refers to the radical $\text{—}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}\text{—OH}$.

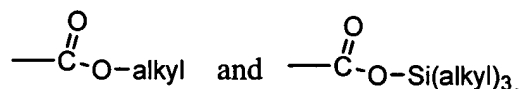
The terms “**halo**” and “**halogen**” and “**halide**”, alone or in combination, refer to chloro, bromo, iodo and fluoro.

The term “**substituted**”, means that one or more hydrogen on the designated
5 atom or substituent is replaced provided that the designated atom’s normal valency is not exceeded, and the that the substitution results in a stable compound. Typical substitutions include, hydroxy, alkyl, alkenyl, acyl, nitro, amino, halo, carboxy, cyano and protecting groups as defined herein. Such substitutions can be further substituted.

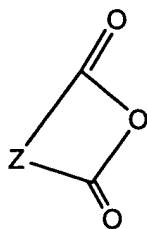
The term “**polar or charged functionality**” refers to a polar or charged group
10 attached in place of one or more hydrogen atoms. Non limiting examples include carboxy, hydroxy, amino, epoxide, etc.

The terms “**heteroaryl**”, alone or in combination, includes an aryl as defined herein containing at least one heteroatom selected from sulfur, oxygen, nitrogen or phosphorus. The heteroaryl may optionally be substituted as that term is used herein
15 and/or substituted with a protecting group as that term is used herein. In addition, adjacent groups on the heteroaryl may combine to form a 5- to 7-membered carbocyclic, aryl, heteroaryl, which in turn may be substituted as above. Nonlimiting examples of heteroaryls are pyrrolidinyl, tetrahydrofuryl, tetrahydrofuranyl, pyranyl, purinyl, tetrahydropyranyl, piperazinyl, piperidinyl, morpholino, thiomorpholino,
20 tetrahydropyranyl, imidazolyl, pyrrolinyl, pyrazolynyl, indolynyl, dioxolanyl, or 1,4-dioxanyl. aziridinyl, furyl, furanyl, pyridyl, pyridinyl, pyridazinyl, pyrimidinyl, benzoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, indazolyl, triazinayl, 1,3,5-triazinyl, thienyl, isothiazolyl, imidazolyl, tetrazolyl, pyrazinyl, benzofuranyl, quinolyl, isoquinolyl, benzothienyl, isobenzofuryl, pyrazolyl, indolyl,
25 isoindolyl, benzimidazolyl, purinyl, carbazolyl, oxazolyl, thiazolyl, benzothiazolyl, isothiazolyl, 1,2,4-thiadiazolyl, isooxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, pyrrolyl, quinazolinyl, quinoxalinyl, benzoxazolyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, xanthinyl, hypoxanthinyl, pyrazole, imidazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,3-oxadiazole, thiazine, pyridazine, triazolopyridinyl or pteridinyl, wherein said
30 heteroaryl can be optionally substituted.

The terms “**protecting group**” or “**protected**” refers to a substituent that protects various sensitive or reactive groups present, so as to prevent said groups from interfering with a reaction. Functional groups that react with Grignard or Lithium reagents can optionally be protected to avoid undesired side reactions. Such protection may be carried out in a well-known manner as taught by Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991 or of the like. The protecting group may be removed after the reaction in any manner known by those skilled in the art. Non-limiting examples of protecting groups include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl or substituted trityl, alkyl groups, acyl groups such as acetyl and propionyl, methanesulfonyl, and *p*-toluenesulfonyl. For example, a protected carboxy could be selected from one of the following:



The term “**carboxylic acid anhydride**”, alone or in combination includes compounds having the formulas acyl-OC(O)R^a, acyl-OC(O)OR^a, acyl-OC(O)SR^a, or acyl-OC(O)NR^aR^b wherein R^a is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, and aralkyl and R^b is selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, alkaryl, aralkyl and a protecting group (as that term is defined herein). The term “**carboxylic acid anhydride**” includes “**cyclic carboxylic acid anhydride**”, which refers to compounds having the formula



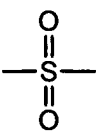
wherein Z is selected from alkyl, alkenyl, alkynyl, aryl, aralkyl and $\text{—(CH}_2\text{)NR}^b$. All “**carboxylic acid anhydrides**” may optionally be substituted as defined herein.

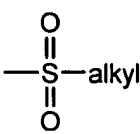
The term “**activated carboxylic acid ester**” includes compounds having the formula C(O)SR” and C(O)OR”, wherein R” is a substituted or unsubstituted aryl or an unsubstituted or substituted alkyl.

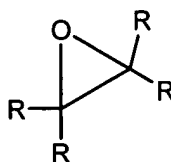
The term “**Grignard Reagent**” generally means an organic magnesium halide (as defined by The Columbia Encyclopedia, Sixth Edition, 2001, herein incorporated by

reference) or a bis-organic magnesium compound represented by the formulas $R^{\gamma}MgX$ and $R^{\gamma}MgR^{\delta}$ respectively, wherein R^{γ} and R^{δ} are independently selected from the group consisting of a primary, secondary, or tertiary alkyl; alkenyl; alkynyl; aralkyl; heteroaryl; and aryl, all of which can be substituted as that term is defined herein, and X is

5 represented by a halide.

The term “**sulfonyl**” refers to the radical .

The term “**alksulfonyl**” refers to the radical .



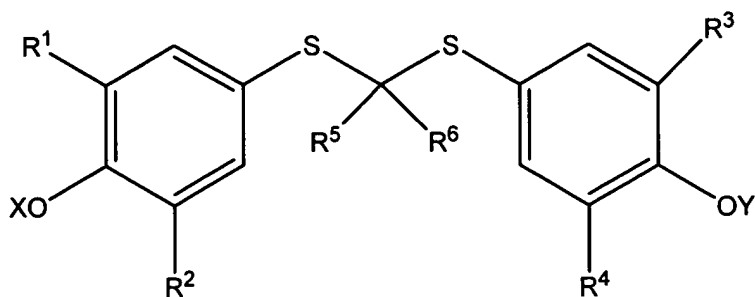
The term “**epoxide**” includes , wherein all R groups are

10 independently selected from hydrogen, alkyl, aryl and arylalkyl wherein said alkyl, aryl and arylalkyl may optionally be substituted with a polar functionality.

The terms “**esters of probucol**” and “**esters of probucol derivatives**” are defined as probucol or probucol derivatives (as the case may be) wherein one or both of the phenol moieties are acylated. The terms “**monoesters of probucol**” and “**monoesters of probucol derivatives**” are defined as probucol or probucol derivatives (as the case may be) wherein one of the phenol moieties are acylated.

The terms “**ethers of probucol**” and “**ethers of probucol derivatives**” are defined as probucol or probucol derivatives (as the case may be) wherein one or both of the phenol moieties are alkylated. The terms “**monoethers of probucol**” and “**monoethers of probucol derivatives**” are defined as probucol or probucol derivatives (as the case may be) wherein one of the phenol moieties are alkylated.

25 The term “**probucol derivative**” refers to the compound



wherein at least one R^1 , R^2 , R^3 , and R^4 is other than t-butyl and/or one or both of R^5 and R^6 are other than methyl and/or one or both of X and Y are other than hydrogen.

5

EXAMPLES

The following examples are provided to illustrate the present invention and are not intended to limit the scope thereof. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedures can be used to manufacture the desired compounds. The materials required for the embodiments and the examples are known in the literature, readily commercially available, or can be made by known methods from known starting materials by those skilled in the art.

Example 1

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (0.25 g, 2.5 mmol) was added in 1 portion. After aging for 45min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 60% probucol monosuccinate, 13% probucol disuccinate, and 27% probucol.

Example 2

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium bromide
5 (1.0 mL, 1.0 M in THF) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (0.25 g, 2.5 mmol) was added in 1 portion followed by anhydrous THF (0.5 mL). After aging for 1.5 h, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer
10 indicated 55% probucol monosuccinate, 27% probucol disuccinate, and 18% probucol.

Example 3

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) and succinic
15 anhydride (0.25 g, 2.5 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) over 2 min. After aging for 40 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 53% probucol
20 monosuccinate, 17% probucol disuccinate, and 30% probucol.

Example 4

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL
25 anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 5 °C and then succinic anhydride (0.25 g, 2.5 mmol) was added in 1 portion. After aging for 45 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated.
30 Analysis by HPLC of the organic layer indicated 46% probucol monosuccinate, 47% probucol disuccinate, and 7% probucol.

Example 5

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (125.0 mg, 1.25 mmol) was added as a solution in THF (1.5 mL) over 5 min. After aging for 40 min, analysis by HPLC of the reaction mixture indicated 55% probucol monosuccinate, 17% probucol disuccinate, and 28% probucol.

Example 6

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (125.0 mg, 1.25 mmol) was added as a solution in THF (1.5 mL) over 5 min. After aging for 20 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 51% probucol monosuccinate, 32% probucol disuccinate, and 17% probucol.

Example 7

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 60 °C and then succinic anhydride (125.0 mg, 1.25 mmol) was added as a solution in THF (1.5 mL) over 5 min. After aging for 20 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 45% probucol monosuccinate, 45% probucol disuccinate, and 10% probucol.

Example 8

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL
5 anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added as a solution in THF (1 mL) over 5 min. After aging for 45 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and
10 the phases were separated. Analysis by HPLC of the organic layer indicated 59% probucol monosuccinate, 20% probucol disuccinate, and 21% probucol.

Example 9

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet,
15 thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added as a solution in THF (1 mL) over 5 min. After aging for 20 min, the reaction was slowly quenched with 1 N HCl
20 and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 59% probucol monosuccinate, 20% probucol disuccinate, and 21% probucol.

Example 10

25 In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 60 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added as a solution in THF (1
30 mL) over 5 min. After aging for 20 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and

the phases were separated. Analysis by HPLC of the organic layer indicated 59% probucol monosuccinate, 26% probucol disuccinate, and 15% probucol.

Example 11

5 In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 5 mL anhydrous toluene. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added as a solution in THF (1
10 mL) over 5 min. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 54% probucol monosuccinate, 10% probucol disuccinate, and 34% probucol.

Example 12

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet,
15 thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene and 0.5 mL anhydrous hexane. To the resulting solution was added isopropylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added over 5 min. After aging for 45 min, analysis by HPLC of the reaction
20 mixture indicated 57% probucol monosuccinate, 16% probucol disuccinate, and 27% probucol.

Example 13

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet,
25 thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 5 mL anhydrous toluene. To the resulting solution was added cyclopentylmagnesium chloride (0.51 mL, 2.0 M in ethyl ether) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion and aged overnight. Analysis by HPLC of the reaction mixture indicated 47% probucol
30 monosuccinate, 14% probucol disuccinate, and 39% probucol.

Example 14

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 5 mL anhydrous toluene. To the resulting solution was added cyclohexylmagnesium chloride (0.51 mL, 2.0 M in ethyl ether) in 1 portion. The reaction was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion and aged overnight. Analysis by HPLC of the reaction mixture indicated 48% probucol monosuccinate, 14% probucol disuccinate, and 38% probucol.

Example 15

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene. To the resulting solution was added benzylmagnesium chloride (1.02 mL, 1.0 M in ethyl ether) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion and aged overnight. Analysis by HPLC of the reaction mixture indicated 50% probucol monosuccinate, 14% probucol disuccinate, and 36% probucol.

Example 16

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 60 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion. After aging for 30 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 57% probucol monosuccinate, 17% probucol disuccinate, and 28% probucol.

Example 17

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion. After aging for 30 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 53% probucol monosuccinate, 11% probucol disuccinate, and 36% probucol.

Example 18

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene and 2.0 mL anhydrous tetrahydrofuran (THF). To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion. After aging for 30 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 55% probucol monosuccinate, 24% probucol disuccinate, and 21% probucol.

Example 19

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous toluene and 2.0 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to room temperature and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion. After aging for 30 min, the reaction was slowly quenched with 1 N HCl and diluted with EtOAc. The biphasic reaction was then cooled to room

temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 50% probucol monosuccinate, 9% probucol disuccinate, and 41% probucol.

Example 20

5 In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 4.5 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (75.0 mg, 0.75 mmol) was added in 1 portion. After aging for 30 min,
10 analysis by HPLC of the reaction mixture indicated 45% probucol monosuccinate, 7% probucol disuccinate, and 48% probucol.

Example 21

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet,
15 thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 50 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 30 min, analysis by HPLC of the reaction mixture indicated 52% probucol monosuccinate, 7%
20 probucol disuccinate, and 41% probucol.

Example 22

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 2.5 mL
25 anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 30 min, analysis by HPLC of the reaction mixture indicated 51% probucol monosuccinate, 7% probucol disuccinate, and 42% probucol.

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Example 23

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 1 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 57% probucol monosuccinate, 9% probucol disuccinate, and 34% probucol.

Example 24

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 1 mL anhydrous anisole. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 58% probucol monosuccinate, 10% probucol disuccinate, and 32% probucol.

Example 25

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 0.5 mL anhydrous anisole. To the resulting solution was added 2-methoxyphenylmagnesium bromide (1.02 mL, 1.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 42% probucol monosuccinate, 6% probucol disuccinate, and 52% probucol.

Example 26

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 0.5 mL anhydrous anisole. To the resulting solution was added 3-methoxyphenylmagnesium

bromide (1.02 mL, 1.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 45% probucol monosuccinate, 5% probucol disuccinate, and 50% probucol.

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Example 27

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 1 mL anhydrous toluene. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After slowly quenching the reaction with 1 N HCl and diluting with EtOAc, the biphasic reaction was cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer indicated 50% probucol monosuccinate, 8% probucol disuccinate, and 42% probucol.

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Example 28

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 1 mL anhydrous THF. To the resulting solution was added octylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 53% probucol monosuccinate, 12% probucol disuccinate, and 35% probucol.

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Example 29

In a dry 25 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (0.25 g, 0.48 mmol) followed by 0.25 mL anhydrous THF. To the resulting solution was added benzylmagnesium chloride (0.51 mL, 2.0 M in THF) in 1 portion. The reaction temperature was brought to 40 °C and then succinic anhydride (55.0 mg, 0.55 mmol) was added in 1 portion. After aging

30

for 45 min, analysis by HPLC of the reaction mixture indicated 50% probucol monosuccinate, 7% probucol disuccinate, and 43% probucol.

Example 30

- 5 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous tetrahydrofuran (THF). To the resulting solution was slowly added benzylmagnesium chloride (10.08 mL, 2.0 M in THF) over 2 min. Once addition was complete the reaction temperature was brought to 40 °C and then succinic anhydride (1.1 g, 10.99 mmol) was added in 1 portion. After aging for 15 min, analysis by HPLC of the reaction mixture indicated 58% probucol monosuccinate, 10% probucol disuccinate, and 32% probucol.

Example 31

- 15 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous tetrahydrofuran (THF). To the resulting solution was slowly added octylmagnesium chloride (10.06 mL, 2.0 M in THF) over 2 min. Once addition was complete the reaction temperature was brought to 40 °C and then succinic anhydride (1.1 g, 10.99 mmol) was added in 1 portion. After slowly quenching the reaction with 1 N HCl and diluting with EtOAc, the biphasic reaction was cooled to room temperature and the phases were separated. Analysis by HPLC of the reaction mixture indicated 53% probucol monosuccinate, 8% probucol disuccinate, and 39% probucol.

Example 32

- 25 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (9.91 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to 40 °C and then succinic anhydride (1.03 g, 10.29 mmol) was added in 1 portion. After
- 30

aging for 15 min, analysis by HPLC of the reaction mixture indicated 56% probucol monosuccinate, 9% probucol disuccinate, and 35% probucol.

Example 33

- 5 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 10 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (9.88 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
10 40 °C and then succinic anhydride (0.965 g, 9.64 mmol) was added as a THF (10 mL) solution over 45 min. After aging for 45 min, analysis by HPLC of the reaction mixture indicated 58% probucol monosuccinate, 8% probucol disuccinate, and 34% probucol.

Example 34

- 15 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (10.8 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
20 40 °C and then succinic anhydride (1.03 g, 10.29 mmol) was added in 1 portion. After aging 45 min, analysis by HPLC of the reaction mixture indicated 52% probucol monosuccinate, 6% probucol disuccinate, and 42% probucol.

Example 35

- 25 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (8.9 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
30 40 °C and then succinic anhydride (1.03 g, 10.29 mmol) was added in 1 portion. After

aging 45 min, analysis by HPLC of the reaction mixture indicated 56% probucol monosuccinate, 11% probucol disuccinate, and 33% probucol.

Example 36

- 5 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (8.2 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
10 40 °C and then succinic anhydride (1.03 g, 10.29 mmol) was added in 1 portion. After aging 40 min, analysis by HPLC of the reaction mixture indicated 52% probucol monosuccinate, 11% probucol disuccinate, and 37% probucol.

Example 37

- 15 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 20 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (7.5 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
20 40 °C and then succinic anhydride (1.03 g, 10.29 mmol) was added in 1 portion. After aging 40 min, analysis by HPLC of the reaction mixture indicated 48% probucol monosuccinate, 10% probucol disuccinate, and 42% probucol.

Example 38

- 25 In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 10 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (9.86 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to
30 40 °C and then succinic anhydride (1.03 g, 10.28 mmol) in THF (10.2 mL) was added over 30 min. After slowly quenching the reaction with 4 N HCl, the biphasic reaction

was cooled to room temperature and the phases were separated. Analysis by HPLC of the organic layer at this point indicated 64% probucol monosuccinate, 13% probucol disuccinate, and 23% probucol.

5 **Example 39**

In a dry 50 mL 3-neck round bottom fitted with a reflux condenser, nitrogen inlet, thermocouple and stir bar was charged probucol (5.0 g, 9.67 mmol) followed by 10 mL anhydrous tetrahydrofuran (THF). To the resulting solution was slowly added benzylmagnesium chloride (9.86 mL, 2.0 M in THF) at such a rate to maintain the
10 internal reaction temperature between 40-50 °C. Once addition was complete the reaction temperature was brought to 40 °C and then succinic anhydride (1.03 g, 10.28 mmol) in THF (10.2 mL) was added over 30 min. Analysis by HPLC of the reaction mixture indicated 64% probucol monosuccinate, 13% probucol disuccinate, and 23% probucol. After slowly quenching the reaction with 4 N HCl, the biphasic reaction was
15 cooled to room temperature and the phases were separated. The organic cut was diluted with THF and water and then the phases were separated again.

After washing the THF cut with 5 N NaOH, the THF solution was azeotropically dried under reduced pressure at 45 °C with the addition of dry THF. Following a solvent switch to heptane, the resulting slurry was cooled to 0 °C with stirring and vacuum
20 filtered. The residue is washed with cold heptane and to the wet cake is added *tert*-butylmethyl ether (MTBE) with stirring. The resulting slurry was filtered and the residue washed with fresh MTBE. The MTBE filtrates were then combined and washed sequentially with 1 N HCl and water. The organic cut was then solvent switched to heptane at 70 °C under reduced pressure. The heptane solution was cooled to 5 °C over
25 45 min and the resulting slurry was filtered, washed with cold heptane and dried to yield 3.42 g MSP (57.3% yield, 97 LCAP) as a white solid, m.p. 139-142°C. ¹H-NMR (300 MHz, CDCl₃): 7.62 (s, 2 H), 7.45 (s, 2 H), 5.37 (s, 1 H), 3.00 (t, 2 H, *J* = 6.8 Hz), 2.78 (t, 2 H, *J* = 6.8 Hz), 1.46 (s, 6 H), 1.44 (s, 18 H), 1.34 (s, 18 H).

Example 40

In a dry 10 mL round bottom fitted with nitrogen inlet, thermocouple and stir bar was charged probucol (1.0 g, 1.93 mmol) followed by 4 mL anhydrous THF. To the resulting solution was slowly added *n*-butyl lithium (1.58 mL, 2.5 M in hexanes) at such a rate to maintain the internal reaction temperature between 40-52 °C. Once addition was complete additional THF (2 mL) was added and the reaction temperature was brought to 40 °C. Solid succinic anhydride (0.20 g, 2.00 mmol) was added to the resulting solution in 1 portion. After aging for 15 min, analysis by HPLC of the reaction mixture indicated 15% probucol monosuccinate, 4% probucol disuccinate, and 81% probucol.

Example 41

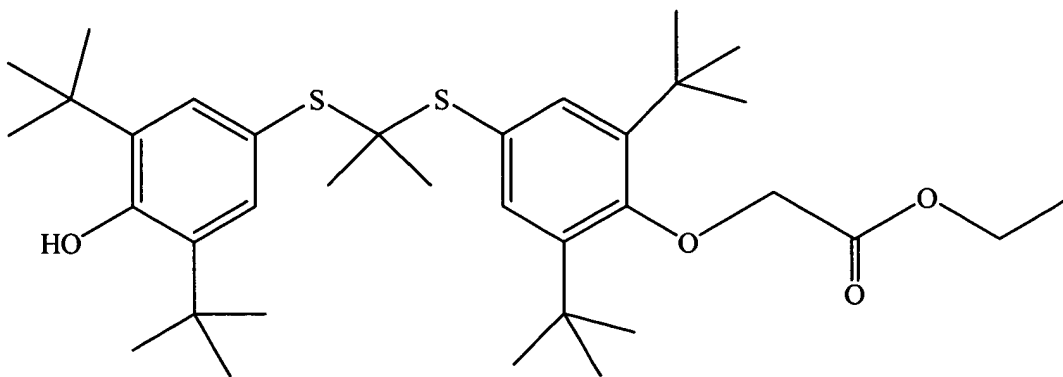
In a dry 10 mL round bottom fitted with nitrogen inlet, thermocouple and stir bar was charged probucol (1.0 g, 1.93 mmol) followed by 4 mL anhydrous THF. To the resulting solution was slowly added hexyl lithium (1.70 mL, 2.3 M in hexanes) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete additional THF (2 mL) was added and the reaction temperature was brought to 40 °C. Solid succinic anhydride (0.20 g, 2.00 mmol) was added to the resulting solution in 1 portion. After aging for 15 min, analysis by HPLC of the reaction mixture indicated 20% probucol monosuccinate, 5% probucol disuccinate, and 75% probucol.

Example 42

In a dry 10 mL round bottom fitted with nitrogen inlet, thermocouple and stir bar was charged probucol (1.0 g, 1.93 mmol) followed by 4 mL anhydrous THF. To the resulting solution was slowly added hexyl lithium (1.70 mL, 2.3 M in hexanes) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete DMF (2 mL) was added and the reaction temperature was brought to 40 °C. Solid succinic anhydride (0.20 g, 2.00 mmol) was added to the resulting solution in 1 portion. After aging for 15 min, analysis by HPLC of the reaction mixture indicated 18% probucol monosuccinate, 1% probucol disuccinate, and 81% probucol.

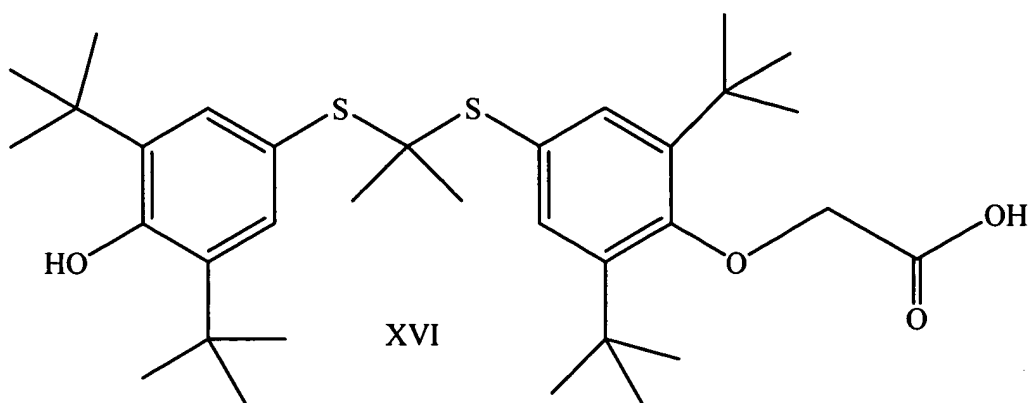
Example 43

In a dry 10 mL round bottom fitted with nitrogen inlet, thermocouple and stir bar was charged probucol (1.0 g, 1.93 mmol) followed by 2 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (1.97 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete DMF (4 mL) was added and the reaction was aged at room temperature. Iodoacetic acid ethyl ester (0.24 mL, 2.03 mmol) was added to the resulting solution in 1 portion. The reaction was heated to 60 °C and aged overnight. Analysis by HPLC of the reaction mixture indicated ca. 70% probucol and 30% probucol-acetic acid ethyl ester (a probucol monoether) of the following formula



Example 44

In a dry 10 mL round bottom fitted with nitrogen inlet, thermocouple and stir bar was charged probucol (1.0 g, 1.93 mmol) followed by 2 mL anhydrous THF. To the resulting solution was slowly added benzylmagnesium chloride (1.97 mL, 2.0 M in THF) at such a rate to maintain the internal reaction temperature between 40-50 °C. Once addition was complete DMF (4 mL) was added followed by sodium iodoacetate (0.44 g, 2.12 mmol) and the resulting solution was heated to 60 °C and aged overnight. Analysis by HPLC of the reaction mixture following an acid quench indicated ca. 98% probucol and 2% probucol-acetic acid (a probucol monoether) of Formula XVI



From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.